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Archives of Internal Medicine

VOLUME 57 JANUARY 1936 NUMBER 1

CYSTIC DISEASE OF THE LUNG

HERMAN HENNELL, M.D.

NEW YORK

Air cysts of the lung which produce symptoms sufficient to call clinical attention to their existence must be considered an uncommon condition. Croswell and King [1] have been able to find reports of only 121 cases, including the 108 case reports compiled by Koontz.[2] The fact is, however, that although rarely encountered clinically, cystic disease of the lung not infrequently presents important diagnostic and therapeutic problems. A report, together with a discussion of a group of cases illustrating the clinical features as well as the diagnostic and therapeutic problems which they presented, is therefore warranted.

Most of the publications on the subject have been essentially from the standpoint of the pathology and pathogenesis. In occasional instances case reports have been published dealing with the results of treatment. This paper aims to illustrate some important types of cystic disease of the lung, especially from the point of view of clinical manifestations, diagnostic features and therapeutic approach. In addition, the mechanism underlying the physical signs and symptoms will receive special consideration because it sheds a good deal of light on the general subject of pneumodynamics.

REPORT OF CASES

CASE 1.—A man aged 46 was admitted to the Mount Sinai Hospital on June 27, 1933, because of the occurrence of moderately profuse fresh hemoptyses for ten days. There was little or no associated cough, and no constitutional symptoms were manifest.

The patient stated that on six different occasions during the previous twenty-nine years he had experienced similar episodes of hemoptysis at varying intervals and of variable severity. On each occasion the cough and constitutional symptoms were minimal, and recovery was complete. During the intervening periods he was free from all symptoms of pulmonary involvement.

General physical examination, as well as an examination of the upper respiratory tract and lungs, showed no abnormalities to account for the hemoptysis. All the ordinary laboratory tests gave negative results.

Roentgen examination of the lungs (fig. 1 left) revealed a number of circular and oval cavities in the lower half of each lung which had the appearance

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From the Thoracic Group of the Mount Sinai Hospital.

1. Croswell, C. V., and King, J. C.: Congenital Air Cyst of the Lung: Report of Case, J. A. M. A. **101**:832 (Sept. 9) 1933.

2. Koontz, A. R.: Congenital Cysts of the Lung, Bull. Johns Hopkins Hosp. **37**:340 (Nov.) 1925.

of air cysts. The largest of the cavities, which was situated laterally in the lower lobe of the right lung, was about 2½ inches (6.5 cm.) in diameter and nearly full of fluid.

The hemoptysis ceased shortly after the patient's admission to the hospital, and after a few days he was discharged free from symptoms.

Comment.—In this case hemoptysis was the only manifestation of the condition on seven different occasions over a period of twenty-nine years. It is to be noted that there was no antecedent history of inflammatory pulmonary disease and that there was no evidence in the roentgenogram of inflammatory changes in the pulmonary parenchyma. These facts, as well as the bilateral distribution of the air cysts, suggest a congenital origin of the condition.

Whether the bleeding had its origin in one of the air cysts and its spontaneous arrest was due to compression of the bleeding vessel when

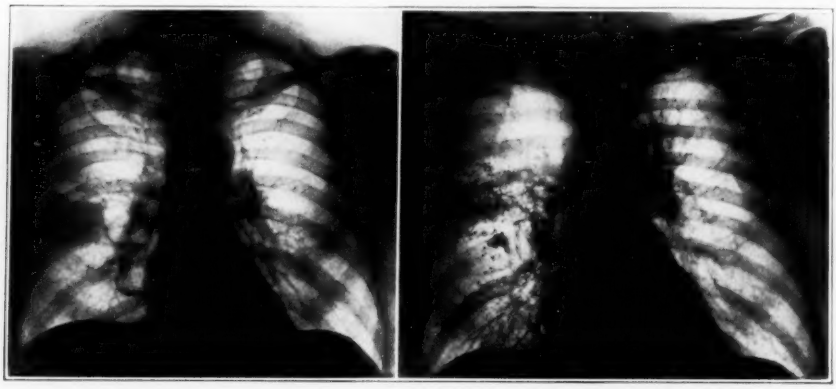

Fig. 1 (case 1).—The figure on the left is a roentgenogram showing a number of circular and oval air cysts in the lower lobe of each lung. The large cyst situated laterally in the lower lobe of the right lung is nearly full of liquid. On the right is a bronchogram in which some of the air cysts are outlined by iodized poppy-seed oil.

the cyst was filled with blood could only be conjectured. It was the blood-filled cyst that was obviously responsible for the dense, round shadow seen in figure 1, and its spontaneous evacuation through the bronchi was demonstrated in the roentgenogram made three days later. The existence of a free bronchial communication with the air cyst in question could have been inferred from the foregoing consideration, and it was demonstrated when iodized poppy-seed oil 40 per cent, which was introduced through the trachea, found its way readily into that cyst (fig. 1, right).

Some of the cysts were not outlined, but that did not exclude the existence of a bronchial communication, as the failure of the iodized

poppy-seed oil to penetrate those cysts may have been due to the tortuosity of the bronchial tract. It is probable that some communication with a bronchus is always present; otherwise the air within a cyst would absorb, and it would collapse. The size of a cyst and the changes which it may show from time to time depend on the character of the bronchial communication. A cyst will remain the same size or will enlarge very slowly if its bronchial communication acts as a two way valve; it will rapidly increase in size, and the intracystic pressure will rise (even to the point of rupture) if the bronchial communication acts as a check-valve. On the other hand, a cyst will collapse if its bronchial communication is shut off and if its air content is gradually absorbed.

From a therapeutic point of view pneumothorax was considered in this case as a method for the control of bleeding from the cyst. The introduction of air into the general pleural cavity, by producing pulmonary relaxation, might result in complete occlusion of the already tortuous tract of communication between the cyst and the bronchial tree. That would lead to the obliteration of the cyst through the absorption of its air content once the source of its continued renewal (open bronchial communication) was abolished. In other words, the induced pneumothorax need not be under high pressure to accomplish the desired effect. Relaxation pneumothorax will, therefore, be tried if hemoptysis recurs. The presence of multiple cysts, as well as the bilaterality of the process, precludes more radical therapeutic procedures, such as surgical extirpation.

This patient has been under observation since his discharge from the hospital. There has been no recurrence of hemoptysis. He has remained in normal health, and the pulmonary status has not shown any change.

CASE 2.—A married woman aged 23 was admitted to the Mount Sinai Hospital on June 15, 1931, having been referred for study because of an obscure pulmonary condition. In 1926 she was confined to a hospital in another city because of signs and symptoms suggestive of a "peculiar" pneumonia, from which she made a complete recovery after about two weeks. She remained well until August 1929, when, three days post partum, she suddenly experienced severe pain in the right side of the chest, associated with moderate dyspnea. There was no cough or fever, and the pain as well as the dyspnea disappeared within twenty-four hours.

The roentgenogram at that time was interpreted as showing spontaneous tension pneumothorax of the right side, probably of tuberculous origin. Though free from symptoms, the patient took a "cure" for ten months, at the end of which period she had gained considerable weight.

For one year previous to admission to the Mount Sinai Hospital the patient felt well except for infrequent episodes of pain in the right side of the chest and dyspnea.

On admission the patient appeared to be in good health, and a general physical examination did not reveal any abnormality. Examination of the chest showed hyperresonance and diminished to absent breathing over the entire right lung as

well as moderate displacement of the heart and mediastinal structures to the left. The left lung did not show any abnormalities. The signs were suggestive either of a tension pneumothorax or of obstructive emphysema of the right lung. In the absence of a history of aspiration of a foreign body or other signs and symptoms of bronchostenosis with a ball-valve type of occlusion, the presence of a tension pneumothorax was considered as more likely. However, bronchoscopic examination would have been necessary in order to establish the differential diagnosis with absolute certainty.

At that point roentgen examination proved most helpful (fig. 2) by showing the presence of an air space in the apex of the right lung, extending to the level of the third rib anteriorly. Below that there were numerous air cysts, some of

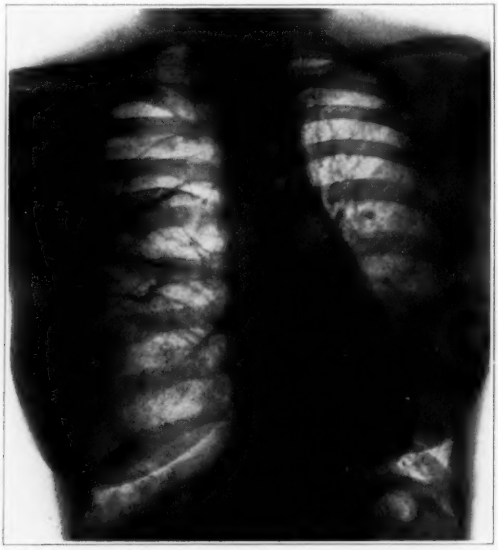

Fig. 2 (case 2).—Roentgenogram showing a large air space (pneumothorax) in the apex of the right lung. Below this there are numerous air cysts. Note the displacement of the heart and mediastinum to the left.

which were several inches in diameter. The right lung extended beyond the midline and displaced the heart and mediastinum to the left. The pleura was thickened over the greater part of the right lung.

A bronchogram showed a displacement of the trachea and of the right main bronchus into the left side of the chest. On the right side only the main branches were outlined. On the left side there was some distortion of the bronchial tree due to the displacement.

Roentgenoscopy disclosed an interesting phenomenon. Since on deep inspiration the air cysts in the right lung were seen to expand and indent the air space in the apical field, there was thought to be an area of pneumothorax rather than a large air cyst in the apex.

One week after admission to the hospital, following an attack of sneezing, the patient experienced a sudden severe pain in the right side of the chest which lasted for a few hours, though the acute phase subsided in a few moments.

The patient was discharged from the hospital eleven days after admission and since then has been under observation for nearly three years. She has continued in normal health except for episodes of mild pain in the right side of the chest, which she has learned to regard with little concern. The pulmonary status has remained unchanged.

Comment.—In this instance of multiple cysts of the right lung there apparently were no symptoms for many years. After 1929 recurring episodes of pain in the chest and dyspnea were the only manifestations. A congenital basis may be assumed in this case because there was no suggestive history prior to 1929, at which time the lesion was known to be fully developed.

The case presented a number of interesting problems. The exact nature of the large air space in the apex of the right lung had to be determined. In the roentgenogram that space looked different from the other air spaces, which were obviously air cysts. Its appearance suggested a localized pneumothorax, and that impression was strengthened by roentgenoscopic evidence, which showed that on deep inspiration the surrounding air cysts indented that air space. The presence of a tension pneumothorax was at first suspected, and it was thought that it might be responsible in part for the displacement of the mediastinum to the left. A manometric reading of the air pressure within the space was therefore taken (an ordinary pneumothorax apparatus being used), and there was found to be a negative pressure of from 8 to 2 cm. of water. The finding of such a high negative pressure confirmed the impression that the air space was a localized pneumothorax, for the air pressure in a pulmonary cyst is either atmospheric or higher and never markedly negative. Since this localized pneumothorax was not under tension, it could not account, even in part, for the marked mediastinal displacement.

The probable mechanism operative in this case was conceived as follows: The displacement of the mediastinum to the left was due to the pressure exerted by numerous distended air cysts in the right lung with an atmospheric or positive intracystic pressure. The positive pressure in some of the air cysts was due to their tortuous bronchial communications, which acted like check-valves. The localized pneumothorax in the apex of the right lung was apparently due to the spontaneous rupture of one of the cysts when its intracystic pressure became relatively too high for the strength of its wall in the presence of a relatively low intrapleural pressure outside the cyst wall. The pneumothorax remained localized because of existing pleural adhesions.

The pneumothorax was chronic and persistent because of the following mechanism: Immediately after the rupture of a cyst the pneumothorax was under considerable pressure (atmospheric or higher), thus sealing off the opening caused by the rupture of the cyst. In the course of time the air in the pneumothorax space was gradually absorbed, with a corresponding fall in pressure. Because of the decreasing intrapleural pressure in the localized pneumothorax, there eventually resulted another spontaneous rupture of the weaker adjacent air cysts, with a renewal of the pneumothorax and repetition of the entire cycle, namely, a recurrent pneumothorax incidental to recurrent rupture of adjacent air cysts.

The associated episodes of pain in the chest and dyspnea depended on the size of the ruptured cyst and the tension of the resulting pneumothorax; hence the varying severity of the symptoms.

From a therapeutic point of view it seemed desirable at first to attempt the further obliteration of the pleural space by injecting irritating fluids and thus preventing the recurrence of the acute episodes of symptoms. However, further consideration led to the conclusion that either the patient had become accustomed to these episodes or the tissues had become insensitive, with the result that the symptoms had become too insignificant to warrant the instituting of any therapeutic procedure which entailed a risk.

The feasibility of the injection treatment of cysts of the lung was demonstrated in the case of a child reported by Croswell and King.[1] They injected iodized poppy-seed oil into the cavity of a huge balloon cyst of the lung. That was followed by a severe inflammatory reaction, with formation of pus which required aspiration. The reaction subsided after a short time and was followed by rapid disappearance of the cyst, with resulting clinical cure of a condition which had previously appeared to be distressing and hopeless.

It is worth mentioning that the logical evaluation of the nature and prognosis of the condition in the present case has made it possible to advise the patient to continue to lead a normal life, without undue restriction, despite the existence of striking changes in the intrathoracic organs.

CASE 3.—A married man aged 46 was admitted to the Mount Sinai Hospital on Feb. 13, 1931, with a history of moderately productive cough for five years not associated with constitutional symptoms. Three months before admission he had a hemoptysis of about 8 ounces (240 cc.) of bright red unclotted blood, followed by expectoration of blood during the subsequent three weeks. The sputum was reported to have contained tubercle bacilli on one occasion. Because of the diagnosis of pulmonary tuberculosis the patient was sent to a sanatorium, where he remained for three months. The observations made at the physical and roentgen examination of the lungs and the uneventful general course were

not typical of clinical pulmonary tuberculosis. Repeated examination of the sputum did not show any tubercle bacilli. The patient was therefore referred to the Mount Sinai Hospital for study and treatment.

On admission the patient's complaints were limited to a slight productive cough and moderate dyspnea on exertion. The results of physical examination of the lungs were inconclusive and merely suggested the presence of moderate fibroid changes in the right lung.

Roentgen examination showed a diffuse fibrotic process involving both lungs, with thickening of the pleura and diaphragmatic adhesions which were not characteristic of tuberculosis. In addition, there was a dense shadow at the root of the right lung extending outward beyond the parasternal line from the level of the fourth to the seventh rib anteriorly. The nature of the shadow could not be definitely determined from its roentgenographic appearance. It was suggestive either of infiltration or of new growth.

Bronchoscopy revealed a crescentic fold running from the lower lip of the right bronchus into the mesial and posterior walls, giving the appearance either of a congenital anomaly or of a healed granulomatous lesion. Specimens taken at various bronchoscopic examinations were reported by the pathologist at one time as cartilage and atrophic mucosa, at another time as showing evidence of nonspecific inflammation and at a later time as showing cells suspiciously like tumor cells.

Bronchography with the aid of iodized poppy-seed oil was not satisfactory. The lateral view showed the bronchi somewhat distorted and pushed posteriorly. The sputum was examined repeatedly, but no tubercle bacilli were observed. The Wassermann reaction of the blood was four plus.

As the bronchial and pulmonary picture could possibly have been due to syphilis, rare as such a condition may be, appropriate therapy was instituted. Under antisyphilitic treatment the patient's condition improved generally, but the roentgenographic appearance of the lungs remained unchanged. The patient left the hospital and was to be followed in the clinic.

A few weeks after his discharge the cough and expectoration became more pronounced. Simultaneously, wheezing was noted, which was suggestive of stenosis of the bronchi of the right lung. Because of the changes in the patient's condition and also because of a suspicion of the presence of tumor cells in the specimen removed during the last bronchoscopic examination, he was readmitted to the hospital on April 30, 1931, for bronchoscopic reexamination. Bronchoscopy was performed in the usual manner. After it was completed, uneventfully, the patient sat up and coughed. Almost immediately thereafter he became unconscious, and the characteristic signs and symptoms of a cerebral lesion, including such manifestations as profound coma, changes in the reflexes, rigidity and convulsive seizure, promptly developed. He died about twelve hours later.

The postmortem examination showed that the right lung was voluminous, owing to the presence of a number of very large, thin-walled air cysts situated mainly subpleurally. The cysts were present in all three lobes, but the middle lobe appeared to be particularly involved. The upper lobe was curiously distorted, having been twisted forward, upward and medially so that it was situated in front of the trachea in the anterior mediastinum. This displacement was due primarily to the pressure of the air cysts in the lateral portion of the upper lobe and to the marked ballooning of the middle lobe, which was almost completely converted into a cystic mass the size of a large grapefruit. Corresponding to the dense hilar shadow seen in the roentgenogram, there was a firm mass, which on section proved to be a large blood clot, in one of the cysts in the upper lobe of the right

lung. The lower lobe showed fewer and smaller air cysts. The pulmonary parenchyma of the right lung showed diffuse and marked fibrosis throughout, leaving little alveolar tissue intact. Widespread pleural adhesions bound the lung firmly to all the surrounding structures.

The bronchi of the right lung presented a distorted appearance. The main bronchus was twisted somewhat irregularly, resulting in a good deal of narrowing. The branch to the middle lobe was directed forward and somewhat upward from its origin so that the normal ridge formed by the origin of the branch to the lower lobe was greatly accentuated and distorted and gave the appearance of a thick crescentic fold which largely occluded its orifice and which corresponded to the bronchoscopic appearance previously described.

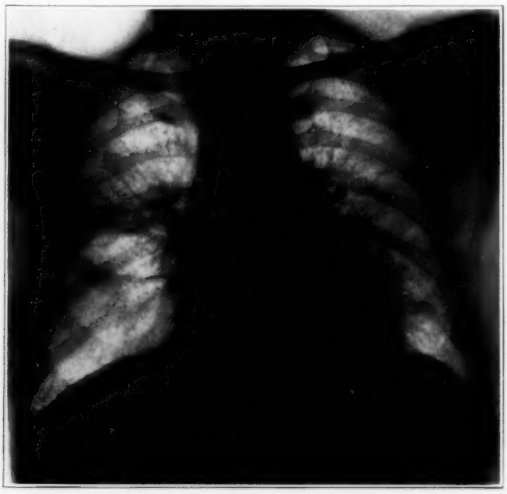

Fig. 3 (case 4).—Roentgenogram showing small shadows scattered throughout both lungs which are suggestive either of "healed" miliary tuberculosis or of pulmonary vascular disease with fibrosis. In the lower lobe of the right lung a large bullous cyst is seen adjacent to an area of marked pulmonary fibrosis.

The left lung also showed extensive fibrosis and pleural adhesions as well as evidence of widespread alveolar emphysema, with a tendency to bullous formation.

The other important change observed was syphilitic mesaortitis. No evidence of bronchoscopic damage was revealed. The autopsy did not include the brain.

CASE 4.—A man aged 65 was admitted to the Mount Sinai Hospital on Dec. 10, 1932, because of three episodes of hemoptysis during the preceding three weeks. Until about eight months before admission he considered himself in normal health. During the subsequent eight months he experienced some weakness, a loss of 30 pounds (13.6 Kg.) in weight, pains in the upper part of the right side of the chest and finally the three episodes of moderate hemoptysis.

On admission the patient appeared to be in fairly good health and coughed only moderately. The temperature was normal.

Physical examination revealed moderate general cardiac enlargement of the hypertensive type. The blood pressure was 220 systolic and 130 diastolic. However, there were practically no signs or symptoms of cardiac decompensation. The significant pulmonary findings included diminished breathing and fine moist râles over the lower lobe of the right lung.

The Wassermann reaction of the blood was negative. Repeated examination of the sputum did not show any tubercle bacilli.

Bronchoscopic examinations did not disclose any obvious cause for the recurring hemoptysis.

The roentgenogram (fig. 3) showed a diffuse fibrotic process throughout both lungs, with the exception of the lower lobe of the right lung, where the appearance was that of bullous emphysema. Whether the process in the lungs

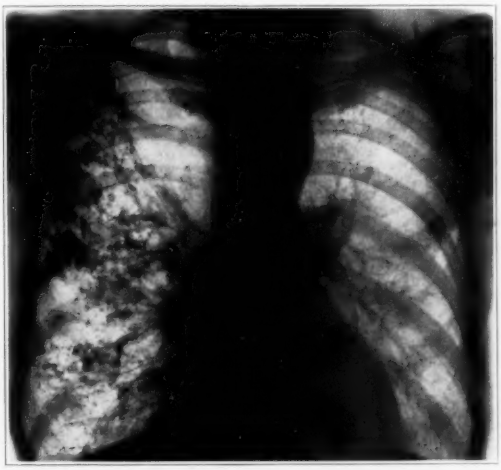

Fig. 4 (case 5).—Roentgenogram showing a large air cyst in the apical portion of the right lung adjacent to an area of fibrosis. The bronchi in the upper lobe are incompletely outlined and are apparently distorted by the air cyst.

was of tuberculous origin or was due to pulmonary vascular disease was not apparent. The association of diffuse pulmonary fibrosis with the bullous type of cystic disease of the lung was well illustrated in this case.

The patient left the hospital after a short, uneventful stay but continued under observation in the clinic. One year later the hemoptysis recurred, but the pulmonary status remained unchanged.

Case 5.—A man aged 60 was admitted to the hematologic clinic of the Mount Sinai Hospital on May 28, 1934, with signs and symptoms suggestive of polycythaemia vera. In Dr. Nathan Rosenthal's opinion the blood picture (hemoglobin, 111 per cent; erythrocytes, 8,250,000; leukocytes, 24,000, and platelets, 1,500,000) as well as the clinical picture were typical of polycythaemia vera. The patient presented no pulmonary symptoms either on admission or at any previous time. However, routine roentgen examination of the lungs disclosed a large air cyst in the apical portion of the right lung adjacent to an area of fibrosis (fig. 4).

Comment.—In case 3 the diagnosis of cystic disease of the lung was not made ante mortem. On the one hand, there were two or three possible causes for the hemoptysis and the pulmonary changes as revealed by various studies, namely, tuberculosis, syphilis and possibly bronchopulmonary neoplasm. On the other hand, nothing was disclosed by the studies to suggest cystic disease of the lung. In cases 4 and 5 the diagnosis was easily made on a clinical basis.

In all three cases cystic disease of the lung was associated with a widespread fibrotic process in the affected lung. The cause of the widespread fibrosis was not apparent. Whatever the etiology of the pleuropulmonary fibrosis, it in turn was undoubtedly responsible for the cystic changes which developed to such a marked degree in case 3 and to a lesser extent in the other two cases. In this connection the pathologic changes in the left lung in case 3 (fibrosis, alveolar emphysema and scattered bullous formation) were most interesting, suggesting an earlier phase in the evolution of a pathologic process similar to the one in the right lung.

As is well known, emphysema results from causes which weaken the normal resistance of the pulmonary parenchyma. It is seen, for instance, in the neighborhood of areas of consolidation or fibrosis in cases of pyogenic or tuberculous bronchopneumonia, where areas of infiltration or fibrosis are usually surrounded by a ring of emphysematous vesicles (so-called compensatory emphysema). At the apex of the lung, along the anterior margins and at the base or in other regions where the pulmonary tissue is poorly supported the emphysema is likely to assume the form of large bullae.

In all these instances there is destruction of alveolar tissue. As a result the adjacent alveoli and alveolar passages are deprived of their former elastic support. Lacking that support, the intra-alveolar pressure causes distention which is progressive and may result in the formation of blebs or bullae of greater or smaller size, depending on the special conditions which prevail locally. The greater the destruction of pulmonary parenchyma, the greater will be the tendency to emphysema and the formation of air cysts.

In case 3 the mechanism of the subsequent changes in the right lung and bronchi was not difficult to recognize. As the air cysts developed and their bronchial communication became more and more tortuous they grew in size, and the intracystic pressure increased by the mechanism previously elucidated (comment on case 1). The pressure of the enlarging, tense cysts was responsible for the marked distortion of the bronchi. Rupture of the cysts, with resulting spontaneous pneumothorax, was precluded in that instance by the widespread pleural obliteration.

The association of the pulmonary changes with the existing polycythemia in case 5 may be purely accidental. It is conceivable, however, that the two conditions may be etiologically related: on the one hand, pulmonary fibrosis, if extensive enough, may lead to secondary polycythemia as well as to the formation of air cysts; on the other hand, pulmonary vascular engorgement or thromboses incidental to polycythemia may lead to pulmonary fibrosis and, secondarily, to the formation of air cysts. One can merely speculate on this phase of the subject until a larger material is available for study.

CASE 6.—A man aged 45 was admitted to the Mount Sinai Hospital on Jan. 26, 1932, because of productive cough of many years' duration. For four months before admission the cough and expectoration had become more severe, the expectoration amounting to about 4 or 5 ounces (120 or 150 cc.) in twenty-four hours. There were no associated constitutional symptoms, and the sputum never had a foul odor.

On admission there were dulness and harsh almost bronchial breathing over the mesial half of the lower lobe of the left lung. The roentgenogram showed bullous emphysema in the lateral portion of the lower lobe. In addition, there was evidence of a chronic pneumonic process as well as of diaphragmatic and pleuropericardial adhesions at the base of the lung.

Bronchoscopy of the left lung revealed that the bronchi were straighter and closer to the median line than normally. Several small elevations were noted over the cartilaginous rings, suggesting kinking of the bronchi due to outside pressure. The bronchi of the lower lobe were dilated, and a small amount of pus was found in them. Injection of iodized poppy-seed oil through the chest wall into one of the blebs, under fluoroscopic control, showed the oil spreading over the emphysematous blebs and entering the dilated bronchi in the lower lobe, thus confirming the diagnosis of cystic disease associated with bronchiectasis in the lower lobe of the left lung.

CASE 7.—A man aged 53 was admitted to the Mount Sinai Hospital on Dec. 14, 1931, for observation because of a history suggesting the presence of a pulmonary abscess.

The patient stated that for many years he had been subject to frequent "colds" with productive cough of short duration. For about seven months before admission, following a "cold," the cough and expectoration continued to increase, the expectoration amounting to 4 ounces (120 cc.) in twenty-four hours. Five months later the sputum had a foul odor for a period of two weeks. Shortly thereafter the sputum was blood-tinged. Night sweats finally began to appear and the patient soon entered the hospital.

Physical examination on admission showed signs of pneumonitis with fibrosis in the lower lobe of the left lung.

Roentgen examination showed pneumonitis in the lower lobe of the left lung. Within the infiltrated area there was a small cavity near the border of the heart at the level of the tenth rib posteriorly. An oblique view showed the presence of several air spaces which had the appearance of air cysts.

Bronchography with the aid of iodized poppy-seed oil (fig. 5) showed marked dilatation of the bronchi in the lower lobe of the left lung. In addition, three collections of the iodized poppy-seed oil (2 by 3 cm.) were interpreted as probably being due to the presence of bronchiectatic cysts.

It was the opinion of those who studied the case that the history was suspiciously like, but not clearly that of, putrid pulmonary abscess, that the various studies established the existence of bronchiectasis in the lower lobe of the left lung, probably associated with cysts of the lung, and that an exploratory operation was justified to determine the exact status of the process.

At operation, performed by Dr. Harold Neuhof, thin pleural adhesions were observed overlying the pneumonic lower lobe of the left lung. After infiltrated lung tissue was traversed a smooth-lined pulmonary cyst containing some mucoid material was entered. A free bronchial communication was present. A primary putrid abscess of the lung was definitely ruled out by the exploration, and the diagnosis of cystic disease of the lung with secondary apparently transient putrid infection was clearly established.

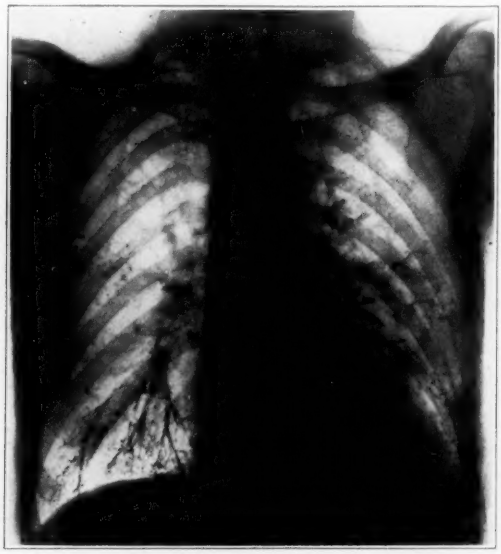

Fig. 5 (case 7).—Roentgenogram showing bronchiectatic air cysts along the left border of the heart partially outlined by iodized poppy-seed oil. The small cavity adjacent to the apex of the heart was shown at operation to be an infected air cyst.

Case 8.—A man aged 22 was admitted to the Mount Sinai Hospital on Jan. 4, 1934, for a study of the pulmonary condition. Following an attack of epidemic influenza in 1918 he was left with a productive cough, which persisted without remission for seventeen years. The sputum was chiefly mucoid and was never foul or blood-tinged. From 1 to 4 ounces (30 to 120 cc.) was expectorated daily. He felt entirely well otherwise and was able to lead a normal life.

On admission a general examination showed a well developed, well nourished man with no abnormalities other than those in the lungs and sinuses. In the right lung there were signs of infiltration in the upper lobe. The left lung was markedly contracted and presented signs of an extensive fibrocavernous process. The sinuses showed bilateral antral suppuration.

Roentgen examination of the chest (fig. 6, left) disclosed a marked deformity of the thorax due to a contraction in the volume of the left lung and scoliosis of the dorsal vertebrae to the left. The left lung had about one-third its normal volume and appeared to be converted into a number of small and large honeycombed cavities, the largest of which was at the apex and measured about 2½ inches (6.5 cm.) in diameter. The heart and mediastinum were displaced to the left. In the upper lobe of the right lung there was also a good deal of fibroid tissue with a number of small cavities within it. Bronchography (fig. 6, right) clearly outlined many of the cavities seen in the ordinary film.

From the physical and roentgen examination it was not possible to make a differential diagnosis between chronic tuberculous and chronic nontuberculous fibrocystic disease of the lung.

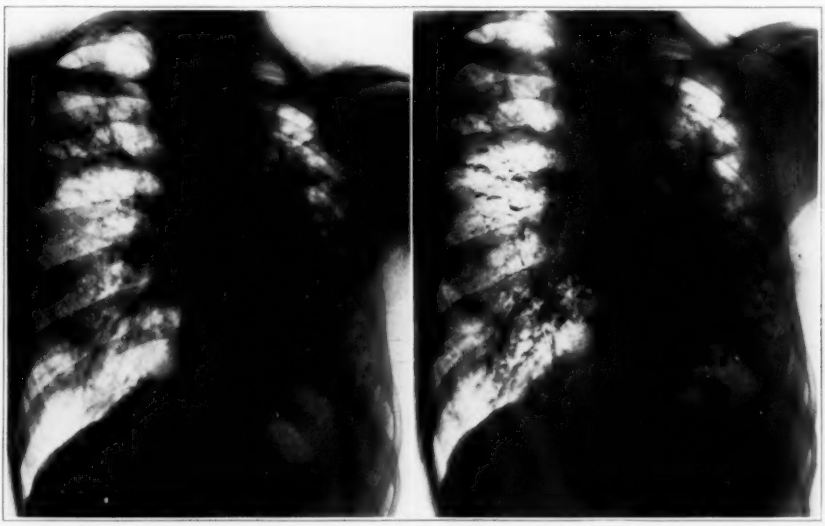

Fig. 6 (case 8).—On the left is a roentgenogram showing a marked shrinkage in the volume of the left lung and numerous small and large honeycombed cavities in it. The right lung also shows considerable fibroid changes as well as a number of cavities. On the right is a bronchogram which shows many of the cavities outlined by iodized poppy-seed oil. Postmortem examination revealed that these cavities represented pulmonary cysts of the bronchiectatic variety.

There was no clubbing of the fingers. The sputum was mucopurulent and showed no tubercle bacilli on repeated tests. From 1 to 6 ounces (30 to 180 cc.) was expectorated in twenty-four hours. The Wassermann reaction of the blood was negative.

During the first twelve days at the hospital the course was uneventful. Then erysipelas of the face developed, associated with marked constitutional symptoms. A few days later metastatic peritonitis developed, and the patient died after five days of acute illness.

At postmortem examination the left lung was observed to be a fibrous mass containing innumerable large and small cystlike cavities communicating with dilated

bronchi and lined in part with bronchial epithelium. There was not much evidence of functioning parenchyma in the left lung. The right lung showed small areas of bullous emphysema as well as bronchiectasis in the peripheral and lateral portion of the upper lobe, which was the seat of considerable fibrosis in the vicinity of a small area of healed tuberculosis. There was also extensive bilateral chronic pleuritis.

Comment.—In cases 6, 7 and 8 cystic disease of the lung was associated with bronchiectasis and chronic pneumonitis of many years' duration. Obviously the chronic bronchopulmonary disease, which was characterized by extensive fibrosis replacing a good deal of the alveolar tissue, was the cause of the bronchiectasis as well as of the associated formation of cysts.

The recent superimposed and apparently transient anaerobic infection of the bronchiectatic cysts in case 7 produced the clinical picture of anaerobic pulmonary abscess. While the various preoperative studies suggested the probable nature of the pathologic process, an exploratory operation had to be resorted to in order to establish the correct diagnosis in that case.

Though a small tuberculous process was found in the upper lobe of the right lung in case 8, it is extremely doubtful if the extensive fibrocystic changes in the lungs could be explained on the basis of the tuberculous infection. It is more likely that the condition had its origin in the influenzal bronchopulmonary infection in 1918, which continued as chronic pneumonitis. The bronchiectatic and cystic disease was the sequel of the progressive destruction of the pulmonary parenchyma. In that instance the changes in the bronchi dominated the pathologic process, and the result was what might be termed the bronchiectatic form of cystic disease (as distinguished from the bullous form illustrated by case 3). In the right lung the process was apparently less advanced, and there bullous as well as bronchiectatic cysts were demonstrated, illustrating the mixed form of the disease.

PATHOLOGY AND PATHOGENESIS

Many theories have been advanced to explain the pathology and pathogenesis of cystic disease of the lung, almost as many as the number of authors who have written on the subject. Most of the theories postulate a congenital or acquired defect in the bronchi. Boyd [3] made no differentiation between the pathogenesis of bronchiectasis and that of cysts of the lung. De Lange [4] expressed the opinion that interference with the development of the alveolar tissue, which leaves the bronchi

3. Boyd, W.: The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1931, p. 191.

4. de Lange, Cornelia: Angeborene Zystenlunge und agenetische Bronchiektasie, Acta pædiat. **6**:352, 1927.

unsupported, is responsible for the dilatation and the formation of cysts. According to Smith,[5] the cysts represent dilated atria. These views are fairly representative of the current opinion on the subject.

Generally speaking, there are two main types of architecture discernible in the structure of air cysts: (1) cysts the origin of which from bronchial dilatations can be readily demonstrated by the concentric arrangement of muscle fibers in the walls or the deposit of cartilage in them or by the lining of stratified ciliated columnar epithelium, and (2) cysts which resemble emphysematous blebs in appearance, essential structure and distribution. Between these two main types of cystic architecture there are all gradations of transitional forms in which both architectural patterns are intermingled to a greater or lesser degree.

The cysts may be solitary or multiple. The solitary or balloon cysts are usually encountered in infancy or early childhood and are rare. They are large and are usually fatal in early life. The multiple cysts are much more common; as a rule they produce relatively few or no symptoms and may be discovered only accidentally later in life. The cysts may vary greatly as to size, distribution, type of bronchial communication and nature of the contents. They may be small or large; they are usually confined to one lung but may be distributed in both; they may communicate with the bronchi either freely or through tortuous channels, and their cavities may be empty or may contain fluid, clear or otherwise. As to age incidence, cystic disease of the lung has been observed in patients of all ages.

From the point of view of origin, two types have been recognized: congenital and acquired. In early childhood the congenital origin of the lesion may not be difficult to establish. It is not always easy to determine whether a lesion is congenital or acquired when seen in an elderly patient. The recognized diagnostic criterion for the congenital origin is the absence of pigment in the involved lung, proving that the affected pulmonary parenchyma never functioned and that the pathologic condition must therefore have antedated birth. However, congenital lesions have occasionally been found adjacent to similar but acquired pathologic processes, as evidenced by the deposition of pigment in the affected pulmonary tissue.

A common associated condition in a cystic lung is pneumonitis and fibrosis of greater or lesser degree. This is invariably present in the acquired forms of the disease, as was shown in the cases which have been described. While pneumonitis and fibrosis are usually the cause of the cystic condition in the acquired form of the disease, it is not

5. Smith, S.: Congenital Cystic Disease of the Lungs, Brit. M. J. **1**:1005 (May 30) 1925.

unlikely that in many cases they may be the result of the associated infection of the cysts.

From a purely clinical point of view this paper is concerned with those forms of cystic disease of the lung, acquired or congenital, which produce symptoms and are likely to present diagnostic and therapeutic problems. The cases discussed in this paper show fairly representative forms of multiple cysts of the lung encountered in later life. The solitary or balloon cyst of the lung, which is usually encountered in infancy, has been described by a number of authors. The condition is characterized by acute episodes of dyspnea and cyanosis. The probable sequence of events was postulated by Parmelee and Apfelbach [6] as follows: There exists at birth a small congenital cyst which presents no signs or symptoms for a variable but usually a short period of time. Progressive enlargement of the cyst takes place in the course of time as a result of the increasing tortuosity of the bronchial communication, with establishment of a check-valve type of bronchial opening. With the rapid increase in the size of the cyst there occurs a corresponding rise in its intracystic pressure, eventually leading to rupture. This results in a spontaneous tension pneumothorax, with marked dyspnea and cyanosis, which may end fatally.

SUMMARY

Cysts of the lung may present baffling diagnostic and therapeutic problems. Eight cases are presented illustrating the clinical features, the diagnosis, the therapeutic problems and the mechanism of the symptoms and signs of the condition. The chief complaints included recurring hemoptysis, episodes of pain in the chest and dyspnea, productive cough and foul expectoration.

Cystic disease of the lung may simulate the following common conditions: benign bronchial bleeding, pulmonary tuberculosis, tension pneumothorax, foreign body obstructive emphysema, bronchial neoplasm with stenosis, putrid pulmonary abscess and bronchiectasis.

The following pneumodynamic mechanisms were analyzed: (1) the development of an air cyst, as determined by aplasia or destruction of the surrounding pulmonary parenchyma, with resultant loss of elastic support; (2) the persistence or spontaneous disappearance of a cyst, as determined by the patency of its bronchial communication; (3) the growth and possible rupture of an air cyst, as determined by a check-valve type of bronchial communication, with a resultant progressive increase in the intracystic pressure; (4) the mechanism of chronic pneumothorax and its relation to recurring cystic rupture; (5) the mechanism of mediastinal displacement and bronchial distortion as pro-

6. Parmelee, A. H., and Apfelbach, C. W.: Congenital Air Cyst of the Lung, Am. J. Dis. Child. **41**:1380 (June) 1931.

duced by large cysts with a high intracystic pressure, and (6) the cause of recurring pain in the chest and dyspnea as related to the rupture of air cysts, with resulting tension pneumothorax.

The congenital and acquired forms of cystic disease were characterized, and the difficulties encountered in their differentiation were pointed out.

The following various types of pulmonary cysts were described: (1) the large "balloon" cysts of early life, which are frequently fatal, and the multiple cysts of adult life, which may produce few or no symptoms; (2) the bullous cysts, the bronchiectatic cysts and the cysts with a mixed type of architecture, and (3) the clean and the infected cysts.

The therapeutic procedures that are feasible in the treatment of the condition together with their rationale were briefly discussed. These included artificial pneumothorax, extirpation of the cysts and the injection of iodized poppy-seed oil or similar substances into the cystic cavity.

CONGENITAL AND FAMILIAL CLUBBING OF THE FINGERS AND TOES, WITH A POSSIBLY INHERITED TENDENCY

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Clubbing of the fingers and toes has been recognized as a clinical manifestation of intrathoracic disease from the earliest times. Hippocrates particularly described the condition as occurring with advanced phthisis and empyema and emphasized the importance of the changes as diagnostic of purulent pleural effusion. Many subsequent authors have described clubbing of the fingers associated with chronic disease of the heart or lungs, but it is still rare in medical literature to find the condition mentioned as being of primary origin. The present case is considered worthy of reporting not only because the simple clubbing of the hands and toes is apparently of primary origin but also because it is familial, possibly hereditary, is congential as far as can be determined from the history and supposedly is the first instance of simple familial and congenital clubbing of the fingers and toes in a Negro to be described in medical literature.

REPORT OF A CASE

The patient was a 44 year old Negro who had done hard labor all his life. He offered no chief complaint, and the clubbing of the fingers and toes was discovered in a routine periodic health examination. Otherwise his general physical condition was entirely normal so far as could be determined by the usual methods of examination. A roentgenogram of the chest presented no evidence of pulmonary or cardiac disease. The Wassermann reaction was negative. The patient stated that he had had the clubbed fingers and toes as long as he could remember and that his mother told him that he had them when he was born.[1] His father (deceased) had similar clubbing, and his mother claimed that the father's condition was also congenital. The condition of the fingers and toes of his grandparents was unknown to the patient or to his mother. The patient had three brothers and one maternal half-brother who presented similar clubbing of the fingers and toes. All claimed to have had the condition as long as they could remember, and the mother stated that the condition was congenital in all. One brother whose fingers and toes were affected had two sons, 17 months and 2 months old. He described the infants' fingers as clubbed, but on examination of the children no true clubbing was found. There was, however, marked enlargement of the volar pads on the tips of the fingers, giving them the appearance of clubbed fingers from the ventral aspect. From the dorsal aspect the nails

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1. The veracity of this statement must be weighed in the light of the Negro's ability to observe pathologic conditions.

presented none of the convexity of true clubbing. Pictures and roentgenograms were made of the infants' hands, and the children will be observed into later life to see whether or not clubbing of the fingers develops. The patient's mother and four sisters presented no clubbing of the fingers or toes.

REVIEW OF LITERATURE

In a review of the literature on primary congenital or familial clubbing of the fingers, reports of fourteen cases were found. As early as 1885 Mangelsdorf [2] reported a case of clubbed fingers without any apparent cause. Fraentzel [3] in 1888 described a case of clubbed fingers in a patient whose father and a healthy sister were likewise affected. In 1891, Freytag [4] observed two cases of primary clubbing of the fingers, in each of which the patient had a healthy father whose fingers were also clubbed. West [5] in 1897 commented on a case of clubbed fingers in a healthy white man aged 38. The clubbing was first noted at the age of 6 years. When the patient was 31 years old the clubbing suddenly, and with no apparent cause, became worse. West also observed clubbed fingers in a healthy woman 50 years old, in whom the condition was supposed to have commenced only three or four weeks previous to examination. In a third case of clubbing he could find no cause. Newton and Mercellis [6] reported a case of simple clubbing of the fingers in a healthy white man, aged 33, with associated hypertrophic osteo-arthropathy. The patient's paternal grandfather, brother, daughter and three dead children (the youngest died when 7 years old) presented the same condition. The patient's father, mother and sister had no clubbed fingers. The clubbing of the digits in this patient had always been proportional to the growth of the hands and feet. Decloux and Lippmann [7] described a patient with congenital primary clubbing of the fingers. One sister had a similar condition. Symons [8] likewise reported a case of primary clubbed fingers. Von Eiselsberg [9] described congenital and familial clubbing of the terminal phalanges in a white man 35 years old. One grandfather, one uncle and one sister of the patient had a similar condition. The author suggested that the origin of the clubbing might be of

2. Mangelsdorf: Wien. med. Wchnschr. **35**:362, 1885.

3. Fraentzel, O.: Ueber Akromegalie, Deutsche med. Wchnschr. **14**:651, 1888.

4. Freytag, A.: Ueber die Trommelschlägelfinger und Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten, Bonn, Hauptmann, 1891.

5. West, S.: Clubbed Fingers, Tr. Clin. Soc. London **30**:60, 1897.

6. Newton, R. C., and Mercellis, E.: A Case of Pulmonary Osteo-Arthropathy, Internat. Clin. **4**:153, 1902.

7. Decloux and Lippmann, A.: Osteo-Arthropathic Hypertrophiante, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:80, 1902.

8. Symons, quoted by Locke.[20]

9. von Eiselsberg: München. med. Wchnschr. **58**:1591, 1911.

a "lymphangiomatous nature." In 1919 Weber [10] saw twin brothers, white, aged 25 years, with clubbed fingers. The toes were not affected and there was no apparent visceral disease associated with the condition. An elder brother, aged 30, had a similar condition. The mother was unaffected; the father's condition was not known; there were no other brothers or sisters. This author reported a second case, in a healthy white man, 25 years old, who had had the clubbed fingers and toes as long as he could remember. His father, three brothers and one sister were similarly affected. Lewy [11] in 1921 noted a case of congenital drumstick fingers. Crouzon and Gutmann [12] described a case of primary clubbed fingers in a white man 30 years old. The patient had always had the condition. His father was also affected. The patient did not know whether his father's condition was congenital or acquired, nor did he know the condition of his father's fingers at the time of the patient's conception. Neurath [13] commented on a case of hereditary clubbing of the thumbs. Recently Kayne [14] reported a case of familial clubbing of the fingers and toes in a white man 32 years old. There were no physical signs of disease of the heart or lungs, and the roentgenogram showed the chest to be normal. The patient had had the condition as long as he could remember. His father and one brother were similarly affected, while his mother, two brothers and three sisters presented no evidence of clubbing. Ragins and Freilich [15] described a case of familial, congenital clubbing of the fingers and toes in a white man 34 years old. One sister, the father and a paternal uncle presented the same condition.

COMMENT

Simple clubbing of the fingers and toes has always been of interest to clinicians, but it was not until the nineteenth century that the subject received sufficient attention to provide any accurate knowledge of the nature of the changes in the extremities and skeleton. Pigeaux [16] in 1832 was the first to use the term "Hippocratic fingers" to describe the condition. No alterations other than those in the fingers were mentioned

10. Weber, F. P.: The Occurrence of Clubbed Fingers in Healthy Persons as a Familial Peculiarity, Brit. M. J. **2**:379 (Sept. 20) 1919.

11. Lewy, E.: Congenital Drumstick Fingers, Med. Klin. **17**:845, 1921.

12. Crouzon, O., and Gutmann: Hereditary Hypertrophic Fingers, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1765, 1931.

13. Neurath, R.: Hereditary Clubbed Thumbs, Wien. klin. Wchnschr. **45**: 1210, 1932.

14. Kayne, G. G.: Familial Clubbing of Fingers and Toes, Proc. Roy. Soc. Med. **26**:270, 1933.

15. Ragins, O. B., and Freilich, E. B.: Familial Congenital Clubbing of Fingers and Toes, Ann. Int. Med. **6**:946, 1933.

16. Pigeaux: Arch. gén. de méd. **29**:174, 1832.

in medical literature until 1889, when von Bamberger [17] described the general thickening and sclerosis of the long bones which is associated with clubbing of the fingers. In a second paper, in 1891,[18] the same author discussed at length the nature and extent of the changes in the bones and their relation to various diseases. In the meantime Marie,[19] in 1890, ignorant of von Bamberger's observations, published a full and accurate description of the process in the long bones and fingers. These two authors, noting especially the subperiosteal formation of new bone rather than the clubbing of the fingers, suggested the cumbersome name "secondary hypertrophic pulmonary osteo-arthropathy" to describe the condition. Since then many equally awkward names have been offered in defining the process of change in the bones, but the original name, hippocratic fingers, has stood the test of time better than the others. Von Bamberger suggested that simple clubbing of the fingers and hypertrophic osteo-arthropathy were closely associated and were probably the same pathologic process, presenting different stages of the same disease. Janeway [20] in 1903 reported several cases of hypertrophic osteo-arthropathy and reviewed all the previous literature, while Locke [21] in 1915 and 1920 brought the survey of the literature up to date. No additional information has been advanced concerning the condition up to the present time, with the exception that Holger,[22] Schirmer [23] and Thomas [24] have suggested the term acropachy to describe the disease in its early stages.

DEFINITION

At the present time hypertrophic osteo-arthropathy may be defined as a disease, generally of secondary nature, occurring in the course of various chronic conditions, characterized by a general and symmetrical hypertrophy of the distal phalanges and toes with resulting clubbing (acropachy), frequently accompanied by enlargement of some of the other bones in the hands and feet or by hypertrophy of the bones of the forearms and legs, and in the late stages, by involvement of the joints.

17. von Bamberger: Wien. klin. Wchnschr. **2**:226, 1889.

18. von Bamberger, E.: Ueber Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten, Ztschr. f. klin. Med. **18**:193, 1891.

19. Marie, P.: De l'ostéo-arthropathie hypertrophiante pneumique, Rev. de méd. Paris **10**:1, 1890.

20. Janeway, T. C.: Hypertrophic Osteo-Arthropathy, Am. J. M. Sc. **126**:563, 1903.

21. Locke, E. A.: (*a*) Secondary Hypertrophic Osteo-Arthropathy and Its Relation to Simple Club Fingers, Arch. Int. Med. **15**:659 (May) 1915; (*b*) Hypertrophic Osteo-Arthropathy, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1920, vol. 4, pt. 2, p. 431.

22. Holger, F.: Ueber Acropachia, Wien. Arch. f. inn. Med. **1**:35, 1920.

23. Schirmer, O.: Acropachia, Wien. Arch. f. inn. Med. **5**:345, 1923.

24. Thomas, H. M., Jr.: Acropachy, Arch. Int. Med. **51**:571, 1933.

The relation of hypertrophic osteo-arthropathy to simple clubbing or hippocratic fingers is interesting. Clubbed fingers exist in almost all of the instances of hypertrophic osteo-arthropathy, but they may also be present in their most characteristic form in association with a considerable number of pulmonary and cardiac diseases in which no involvement of the long bones is to be noted (Thayer [25]). Is the same cause at work in both instances, the one condition being simply a more advanced degree of the other? It is certainly true that the most clearly defined hippocratic fingers may exist entirely alone, while in some cases of well marked hypertrophic osteo-arthropathy the clubbing of the terminal phalanges may be by no means as characteristic. In his second paper von Bamberger [18] discussed the possible relationship of simple clubbing of the fingers to hypertrophic osteo-arthropathy and suggested that the former may be simply an early stage of the latter. The opinions expressed by subsequent authors differ widely. Some have regarded the two conditions as closely related, if not identical, while others have held that there is a distinct difference between the two and that they should be regarded as independent. The evidence is entirely in favor of the opinion that the two conditions are identical and according to Landis [26] may be summarized as follows: (1) The two conditions are found associated with the same group of primary diseases; (2) the type of clubbing in the two conditions is the same, the differences described being merely the result of difference in the stage of the process; (3) clubbing of the fingers invariably occurs in hypertrophic osteo-arthropathy; (4) many conditions which appear to be simple clubbing reveal on roentgen examination alterations in the long bones precisely the same as those seen in hypertrophic osteo-arthropathy.

According to Sternberg,[27] three clinical types of hypertrophic osteo-arthropathy may be described, as follows: (1) Clubbing of the fingers and toes without changes in the long bones and usually without subjective symptoms; (2) a combination of clubbing with painful thickening of the long bones, especially of the lower portion of the forearms and legs (this type was described by von Bamberger [17]); (3) a stage of the disease in which the condition is no longer a mere incident in the course of the primary disease but by reason of the conspicuous general deformities and severe symptoms itself comes to the foreground (Marie's type [19]). These groups, in the light of present knowledge, are clearly only different stages in the development of one disease, hypertrophic

25. Thayer, W. S.: Hypertrophic Pulmonary Osteo-Arthropathy and Acromegaly, New York M. J. **63**:33, 1896.

26. Landis, H. R. M.: Hypertrophic Pulmonary Osteo-Arthropathy, with a Report of Two Cases, Penn. M. J. **10**:852, 1907.

27. Sternberg, M., in Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1903, vol. 7, pt. 2, p. 72.

osteo-arthropathy. Locke [21b] watched the advancement of the process through its different stages. In making the study reported in this paper my interest has been primarily with the first type of the disease, namely, simple clubbing of the fingers and toes without any changes in the long bones.

In the congenital or familial type of clubbing of the fingers, there does not seem to be any progressive tendency of the disease to develop into the hypertrophic osteo-arthropathic type; at least, no such case was reported in the literature. Five cases (Gluzinski,[28] Reed,[29] Soltau,[30] Symons,[8] van der Weijde and Boekhoudt [31]) which were apparently instances of primary hypertrophic osteo-arthropathy were reported up to Oct. 3, 1914 (Locke [21a]), and no mention of a subsequent case was found other than that reported by Thomas,[24] in which the condition followed a subtotal thyroidectomy. The evidence is overwhelming that hypertrophic osteo-arthropathy is secondary to some visceral disease, usually pulmonary or cardiac, yet an occasional case has been reported in which it followed disease of the abdominal viscera, blood dyscrasia or involvement of the thyroid. In the cases in which the phenomena have existed since birth and have been present in other members of the family, one must either beg the question or postulate some peculiar susceptibility of the osseous system. That great individual differences in the reaction of bones to irritants exist is evident from the varying time required for the repair of fractures. In the case reported here, in which the condition was apparently primary and had an inherited or congenital and familial association, there has been no progression of the clubbing process other than the proportional enlargement of the terminal phalanges with the growth of the hands.

Hypertrophic osteo-arthropathy and simple clubbing of the fingers are much more prevalent in men than in women; in Thompson's [32] series they occurred in men in 86 per cent of the cases. That hypertrophic osteo-arthropathy is not necessarily a disease specific to the human race is evidenced by the report of Ball and Lombard,[33] who

28. Gluzinski, A.: Osteo-Arthropathie Hypertrophiante Mariego, Przegl. lek. **1**:480, 1811.

29. Reed, E. P.: Un caso de osteo-arthropatia hipertrofiante de orijen néumico, Rev. méd. de Chile **32**:199, 1904.

30. Soltau: A Case of Chronic Hypertrophic Osteo-Arthropathy, Tr. Clin. Soc. London **34**:249, 1901.

31. van der Weijde, A. J., and Boekhoudt, H. B.: Een geval van ostéo-arthropathie hypertrophiante, Nederl. tijdschr. v. geneesk. **31**:781, 1895.

32. Thompson, H. E. S.: Hypertrophic Pulmonary Osteo-Arthropathy, Med. Chir. Tr., London **87**:85, 1904.

33. Ball, V., and Lombard, C.: Hypertrophic Pulmonary Osteo-Arthropathy in Wild Animals in Captivity, Bull. Acad. de méd., Paris **95**:16, 1926.

observed the condition in a 10 year old captive lioness with pulmonary tuberculosis. Ball and Alamartine [34] described a similar condition in tuberculous dogs.

PATHOLOGIC CHANGES IN CLUBBING OF THE FINGERS

In the average case of simple clubbed fingers, as in this reported case (fig. 1), the deformity is sharply confined to the distal phalanges and is almost strictly symmetrical. The thumbs and forefingers are commonly the first attacked, and hence when the condition has reached an advanced stage they are likely to present a considerably greater degree of deformity than is shown by the other fingers. The most striking feature is the bulbous enlargement of the terminal phalanges of the fingers and toes, which is largely due to changes in the soft parts. The clubbing begins just beyond the interphalangeal joint as a definite firm transverse ridge, most marked on the dorsal aspect but extending onto the lateral surfaces of the fingers. On the palmar side

Fig. 1.—Photograph of the hands of a Negro showing clubbing of the fingers.

the increase in size is more gradual. The whole finger beyond the ridge is bulbous or drumstick-like. The overlying skin is smooth and shiny. The nails are greatly thickened, ridged longitudinally and curved in both directions, sometimes to such an extent as to offer a close resemblance to a parrot's beak. Corper and Cosman [35] described the hyperconvexity of the nail, and Lefebvre [36] likened it to a watch glass fitted on the end of the finger. The nail bed is full, rounded, smooth, cyanotic and injected. The sluggish circulation is apparent from slow return of color after slight pressure on the nail. The base of the nail lies above the level of the knuckle, so that its outline can be discerned

34. Ball, V., and Alamartine, H.: Les lésions broncho-pulmonaries dans l'ostéo-arthropathie hypertrophiante pneumonique du chien: étiologie et pathogénie du syndrome de P. Marie envisagé comme une tuberculose inflammatoire, J. d. méd. vét. et de zootech. **17**:1, 1913.

35. Corper, H. J., and Cosman, P.: Hypertrophic Osteo-Arthropathy in Pulmonary Tuberculosis, Am. Rev. Tuberc. **5**:357, 1921.

36. Lefebvre, A.: Des déformations ostéo-articulaires, consécutives à des maladies de l'appareil pleuro-pulmonaire (osteo-arthropathie hypertrophiante-pneumique de P. Marie), Paris, Félix Alcan, 1891.

beneath the skin. When the nail is pressed at either end, it rocks up and down, giving the impression that it is fastened only at its center and that it is floating. Normally the root of the nail is attached to the phalangeal periosteum. Hyperextension of the terminal phalanx associated with clubbing of the fingers was first described by Marie [19] and has subsequently been reported by other observers. In the early stages of clubbing, slight curving, slight cyanosis and mobility of the nail root occur before the obvious swelling or clubbing. A significant early change is an unusual smoothness or shininess of the skin behind the nail and over the root of the nail.

In a few cases clubbed fingers have been examined microscopically, but no two observers have agreed as to the essential changes in the soft parts. It is not surprising, therefore, that there is considerable difficulty in offering a satisfactory explanation of the manner in which clubbing arises, and this difficulty is certainly not diminished by the extraordinary number of diseases in which the deformity appears. Campbell [37] presented longitudinal photomicrographs of a clubbed finger and noted a distinct thickening of the tissue between the nail and phalanx, due to the presence of excessive edema. The fibrils of the connective tissue, instead of running in compact bundles as in normal fingers, were widely separated from each other in many places. There was no fibrous thickening of the rete mucosum, no increase in the connective tissue (though he stated that if the edema persists long enough increase in the connective tissue will result) and no excess of fat. Campbell [37] concluded that the essential difference between the clubbed and the normal finger was the edematous condition of the tissue lying between the nail bed and the bone. Freytag [4] noted dilatation of the capillary loops in the nail bed, with engorgement of the interpapillary processes, but noted no alteration in the skin, no endarteritis obliterans and no thickening of the nerve sheaths. Thérèse [38] commented on the hypertrophy of the horny layer, papillae, and connective tissue of the derma. Buzzard [39] observed mainly an excess of subcutaneous fat in the bulbous fingers. From the study of a microscopic section of a clubbed finger, Schirmer [23] noted a tissue resembling embryonic mucoid tissue. Thomas [24] observed marked dilatation of the venous side of the capillaries of the nail bed and an extreme degree of tortuosity of the arterial side.

37. Campbell, D.: Hippocratic Fingers, Brit. M. J. **1**:145, 1924.

38. Thérèse, L.: Ostéo-arthrite hypertrophiante pneumonique: Examen histologique et chimique des os de l'avant bras, Bull. Soc. anat. de Paris **66**:143 (Feb.) 1891.

39. Buzzard, E. F.: Sequel to a Case of Pulmonary Hypertrophic Osteo-Arthropathy; Necropsy, Brit. M. J. **1**:1333 (June 1) 1901.

ROENTGENOLOGIC STUDY OF CLUBBED FINGERS

It is generally stated that the typical bulbous enlargement of the terminal phalanges of the fingers and toes is entirely due to changes in the soft parts. This is undoubtedly true in the majority of cases of clubbed fingers in which there are no changes in the long bones, although in a few cases in which roentgen examination was made there was an unmistakable alteration in the distal phalanges. It must be always borne in mind, however, that the ungual phalanges in healthy persons present extreme variations in size and shape. Locke [21a] studied thirty-nine cases of apparently simple clubbing and found that roentgen examination revealed a definite proliferation of the bone of the distal phalanges in five instances. Many other authors (Kessel,[40] Corper and Cosman,[35] Thomas,[24] Gouldesbrough,[41] Singer,[42] Hyman and Herrick [43]) described similar changes as rarely, though definitely, occurring

Fig. 2.—Roentgenogram of clubbed fingers showing spatulation of the bone in the distal half of the terminal phalanges.

in simple clubbed fingers. In the familial type of clubbing of the fingers Ragins and Freilich [15] observed the distal bony phalanges to be enlarged, and Kayne [14] commented on the terminal phalanges being splayed out. In the case reported here definite spatulation of the distal halves of the ungual phalanges was readily noted (fig. 2).

In the more advanced cases in which there are changes in the long bones the hypertrophy of the terminal bones of the fingers is much more common and marked. The age of the patient is also important in noting

40. Kessel, L.: Hypertrophic Osteo-Arthropathy, Arch. Int. Med. **19**:239 (Feb.) 1917.

41. Gouldesbrough, C.: Pulmonary Osteo-Arthropathy, Arch. Roentg. Ray **18**: 208, 1913.

42. Singer, S.: Drumstick Fingers with Peculiar Bony Changes, Wien. med. Wchnschr. **78**:226, 1928.

43. Hyman, C. H., and Herrick, T. P.: Chronic Osteo-Arthropathy in a Child, J. A. M. A. **78**:1043 (April 8) 1922.

any changes of the bone, as periosteal reactions are more easily stimulated in a child. Walters,[44] however, observed fetal clubbing of the fingers (fetal age not given) associated with congenital heart disease, and noted no bony changes. The alterations in the end-phalanges are in the nature of an irregular mossy proliferation confined chiefly to the distal half, giving to the bone a "bur-like" appearance. Rarely, long spurlike projections (osteophytes) are found at the proximal ends of the distal phalanges, near the line of the joint cartilage (Locke [21a]).

Thompson [32] reported that chemical examination of the affected bone in hypertrophic osteo-arthropathy showed a marked increase in magnesium phosphate at the expense of the calcium salts, with increase in the organic matter.

Brooks [45] cited several cases of hypertrophic osteo-arthropathy with bulbous enlargement of the nose and thickening of the subcutaneous tissues of the malar regions. No such changes were observed in the case of simple clubbing reported here. Corper and Cosman,[35] when studying clubbing of the fingers in pulmonary tuberculosis, observed in many instances a peculiar nodular tumor on the hard palate in the midline, extending to the junction of the hard and the soft palate. There were no symptoms except change of speech, although roentgen examination revealed changes of the bone in the maxilla and hard palate. No such changes were noted in the case reported here.

ETIOLOGY

The etiology of simple clubbing of the fingers and toes and of hypertrophic osteo-arthropathy has been a cause of concern to clinicians for many years. As early as 1832 Pigeaux [16] considered clubbing of the fingers as due to a local circulatory disturbance with a consequent edematous swelling and heaping up of the nail matrix. He thought that if the nail matrix was raised above the nail bed the nail must grow downward toward the palmar surface of the finger. That dilatation of the capillaries in the nail bed occurs in simple clubbing of the fingers is generally accepted. The continued peripheral hyperemia is produced by compression of the capillaries of the lung or by obstruction of the venous return. The capillaries, already being subjected to increased hydrostatic pressure, become chronically engorged. The hyperemia gives the extremities their cyanotic appearance and later brings about a proliferation of the distal phalanges of the fingers and toes. The capillaries supplying the phalangeal periosteum may be the first to

44. Walters, F. R.: A Case of Hyperplastic Osteo-Arthritis, or Pulmonary Hypertrophic Osteo-Arthropathy of Marie, St. Thomas's Hosp. Rep. **24**:105, 1897.

45. Brooks, H.: A Discussion of the Pathogenesis of Hypertrophic Pulmonary Osteo-arthropathy, New York M. J. **94**:608, 1913.

become involved, with resultant fibroblastic and osteoblastic stimulation, and the deposition of the layer of subperiosteal new bone typical of hypertrophic osteo-arthropathy. The digital pulp undergoes an increase, giving the fingers their typical drumstick appearance.

In support of the theory that venous obstruction, with resultant capillary hyperemia, is the cause of clubbing of the fingers, Campbell [37] cited instances in which elevation of the limb for several days reduced the clubbing while ligation of the subclavian artery almost caused the clubbing to disappear. Souques [46] reported a case of unilateral clubbing in which the veins in the arm above were markedly varicose, and Thomas [24] commented on clubbing resulting from alteration of the circulation in sudden reduction of the metabolic rate. Even though it may be objected that clubbing of the toes is not a sequel to unilateral thrombophlebitis, the theory that mechanical obstruction is the sole etiologic factor of clubbing is difficult to accept. In the first place, clubbing is not edema, and it is hardly ever noted in association with edema, or in cases in which cyanosis and central obstruction are considerable, as in diseases of the heart other than congenital disorders, intrathoracic tumors, etc. Clubbing occurs in many cases of thoracic disease in which there is no obvious interference with the circulation, as in chronic empyema, and occasionally in abdominal conditions in which the thorax is entirely free from disease. It may occur in persons who are otherwise in perfect health (West [5]).

That defective oxygenation of the blood may also play a rôle in clubbing is possible, since it is well known that suboxygenated blood or passive congestion invites hyperplasia of abnormal tissue, as witness the interstitial hyperplasia in chronic congestive diseases of the liver and spleen. This conception is capable of wider application and will explain the clubbing so frequently seen in cases of congenital heart disease. In this condition clubbing occurs more especially in cases of pulmonary stenosis, with a patent foramen ovale and an incomplete intraventricular septum. It is to be noted that congenital disease is the condition most frequently associated with cyanosis. Anoxemia also explains the clubbing associated with dyscrasias of the blood, and the "autotoxic enterogenous cyanosis" (Campbell [37]), in which there is either methemoglobin or sulfhemoglobin in the blood resulting from the absorption of the products of intestinal putrefaction.

An objection can be made against anoxemia as the cause of clubbing. If an insufficient supply of oxygen to the tissues is an important etiologic factor in clubbing, why has clubbing not been found in cases of long standing severe anemia? Thomas [24] suggested that it may be that the

46. Souques, A.: Pathogenesis of Hippocratic Fingers, Bull. et. mém. Soc. méd. d. hôp. de Paris **43**:186, 1919.

adjustment of tissues to anemia is gradual, whereas in simple clubbing time for this adjustment is lacking.

Marie [19] strongly advocated the theory that clubbing is due to toxins. He summarized the cycle of changes under three headings: (1) A lesion of the respiratory apparatus, allowing the production of putrid or fermenting substances under the influence of micro-organisms; (2) the absorption and passage of these products into the general circulation; (3) an elective action of these substances on certain parts of the bones and joints.

It is evident from the fact that the disease occurs in association with certain lesions of the heart and with other conditions in which no form of suppuration exists that the theory that clubbing is due to circulating toxins alone will not fit all cases. It is also important to point out other obvious objections in considering circulating toxins the cause of clubbing. Thomas [24] asked why, for instance, an abscess of the lung should produce such a toxin if abscesses elsewhere in the body do not produce it. Why should clubbing occur with carcinoma of the bronchus and not with carcinoma in other parts of the body? Why should the toxin be liberated in pulmonary tuberculosis and not in tuberculosis of other organs?

Béclère [47] has combined the two theories of clubbing into a mechano-toxic hypothesis. He considered that venous blood naturally contains substances which provoke changes in the fingers and that if during its passage through the lungs these substances are not removed from the blood clubbing results.

The occasional association of clubbing of the fingers with certain nervous diseases has suggested a possible relationship between hypertrophic osteo-arthropathy and diseases of the nervous system. Several authors (Hirshfeld,[48] Janeway [20] and Mobius) have written in favor of such an etiologic relationship. Wynn [49] observed no gross lesion of the central nervous system in the cases cited and in the few instances in which the nerves had been especially examined. Any changes found have been easily explained. Moreover, in those cases of clubbing of the fingers associated with neuritis due to injury there were always marked trophic changes in the skin which did not occur in cases of simple clubbing.

Godlee [50] regarded hypertrophic osteo-arthropathy as due to syphilis, but later writers have been unable to find sufficient evidence for such

47. Béclère, A.: Semaine méd. **21**:94, 1901.

48. Hirshfeld: Ueber Vergrösserungen der Hände und Füsse auf neuritischer Grundlage, Ztschr. f. klin. Med. **44**:5 and 251, 1902.

49. Wynn, W. H.: Secondary Hypertrophic Pulmonary Osteo-Arthropathy, Birmingham M. Rev. **55**:139, 1904.

50. Godlee, H. J.: Bone and Joint Changes in Connection with Thoracic Disease, Brit. M. J. **2**:57, 116 and 1417, 1896.

a claim. Thorburn [51] suggested that clubbing is actually of a tuberculous nature, but "of a benign type, having no tendency to break down and caseate." Massalongo [52] expressed the belief that clubbing is the "consequence of causes acting contemporaneously or alone, among which the arthritic diathesis plays the principal rôle."

Cummins [53] demonstrated the presence of volar padding of the terminal phalanges in the third fetal month. In the last half of gestation regression occurs, which results in contours of the hand comparable to those of the adult. Persistence of the volar pads into infant life, as seen in the nephew of the patient described here, might offer a possible explanation of congenital clubbing.

Higier [54] observed in Warsaw, in the last half of 1917, seventy cases of osteo-arthropathy, osteomalacia and late rachitis in an endemic form. He thought that lack of vitamin A was the cause.

Thayer,[25] Ronchetti,[55] and others compared hypertrophic osteo-arthropathy to amyloid degeneration, which in certain unexplained conditions follows or accompanies protracted suppuration.

Clubbing is manifestly more likely to be carried on to a marked degree in young tissues, which are physiologically most inclined to hyperplastic growth. Hence it is that the changes due to clubbing are more pronounced in youth than in adult life or in old age.

From all of the theories as to the etiology of clubbing, it is most generally accepted that clubbing is the result of altered flow of blood, defective oxidation or hyperemia in the tissues of the extremities, whether produced mechanically by obstruction to venous return or as a result of a general lowering of the oxygen tension of the blood affecting parts of the body where normally circulation is slow. The altered flow of blood offers itself as the most plausible common etiologic factor.

Considering the difficulty of explaining the etiology of clubbing of the fingers secondary to some visceral disease, it is readily understood that the etiology of primary clubbing is all the more vague, especially in cases in which the condition is apparently congenital and definitely familial.

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51. Thorburn, W.: Three Cases of Hypertrophic Pulmonary Osteo-Arthropathy, Brit. M. J. **1**:1155, 1893.

52. Massalongo, R.: Osteo-artropatia ipertrofica pneumica, Policlinico (sez. med.) **4**:512, 1897.

53. Cummins, H.: The Topographic History of Volar Pads (Walking Pads; Tastwallen) in The Human Embryo, Contrib. Embryol. (no. 113) **20**:103 (Jan.) 1929.

54. Higier, H.: Endemic Osteo-Arthropathy, Ztschr. f. klin. Med. **95**:445, 1922.

55. Ronchetti, V.: Club Fingers and Leukocytosis as Symptoms of Hepatic and Amyloid Degeneration, Osp. maggiore **18**:1 (Jan.) 1930.

EXPERIMENTAL STUDY

A limited amount of experimental work has been done to produce clubbed fingers. Wegner (cited by Locke [21a]) showed that small doses of phosphorus caused a formative stimulation of the periosteum. Similar results were obtained by Gil (cited by Locke [21a]) in animals fed arsenic. Von Bamberger [18] attempted to produce the lesions of hypertrophic osteo-arthropathy in rabbits by injecting bronchiectatic sputum into the rectum, but his results were negative. Herz,[56] by experimentally widening the capillaries of the nail bed, produced clubbing of the fingers. Campbell,[37] as noted previously, observed that elevation of the arm for several days reduced the clubbing, while ligation of the subclavian artery almost entirely removed it. Compere, Adams and Compere [57] were unsuccessful in reproducing periosteal changes in dogs when paraffin had been injected into the lungs.

ONSET AND PROGNOSIS

Clubbing of the fingers usually is of insidious onset, yet Ebstein [58] has noted its appearance within a single week. Pain, lividity and numbness of the finger-tips accompanied the rapid onset. West [5] reported a case in which clubbing developed in two weeks.

The prognosis of the condition is dependent entirely on the course of the primary disease. Often there is a characteristic irregular clinical course of exacerbations and remissions following increased activity or improvement in the primary disease. The fluctuations in local signs are largely due to changes in the soft parts, although it is possible that in many instances a similar variation, but of less marked degree, takes place in the osseous tissue as well (Locke [21a]). It has been reported that in some of the early and acute cases of clubbing complete regression has been observed with cure of the primary disease. It is probable, however, that when the hypertrophic osteo-arthropathy has passed the first stage the retrogression is never complete.

In the case of possibly inherited, congenital and familial clubbing reported here and in similar cases reported in the literature, there has been no progressive or regressive tendency of the process. This type of clubbing, once it has occurred, appears to be limited in its progressive development but is permanent.

CONCLUSION

As West [5] has so aptly described the condition, clubbing is one of those phenomena with which all physicians are so familiar that they appear to know more about it than they really do.

56. Herz: Verhandl. kong f. inn. Med., 1896, p. 466.

57. Compere, E. L.; Adams, W. E., and Compere, C. L.: Possible Etiological Factors in the Production of Pulmonary Osteo-Arthropathy, Proc. Soc. Exper. Biol. & Med. **28**:1083 (June) 1931.

58. Ebstein, E.: Deutsches Arch. f. klin. Med. **89**:67, 1907.

EFFECT OF ERGOTAMINE TARTRATE ON PRESSURE OF CEREBROSPINAL FLUID AND BLOOD DURING MIGRAINE HEADACHE

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During the last few years a half-dozen reports have appeared in the French and German literature concerning the value of ergotamine tartrate (gynergen) in the treatment of migraine. A summary of the literature as well as of the therapeutic results obtained with forty-five of his own patients has been made recently by Lennox.[1] All the authors who have studied the subject agree that in the great majority of patients suffering from migraine headache the injection of ergotamine tartrate cuts short the attack, an action which seems to be specific, or nearly so, for headache of the migraine type.

The authors who have reported these dramatic clinical results have offered theories but little or no evidence concerning the mechanism by which ergotamine acts. A study of the physiologic effects of ergotamine on patients during a migraine headache might, we thought, uncover the cause of the relief and hence suggest the cause of the migraine. With this thought in mind, we have observed the effects of ergotamine tartrate on the pressure of the cerebrospinal fluid and of the arterial blood, on the rate of the heart and on the symptoms of patients who were suffering from an attack of migraine. As a control, similar observations were made on a group of patients not subject to migraine.

Ergotamine is the most recently isolated active principle of ergot, having been separated from ergot in 1918 by Stoll.[2] A specific alkaloid with the formula $C_{33}H_{35}N_5O_5$, it is similar to, though not identical with, ergotoxine $C_{35}H_{41}N_5O_6$.[3] Ergotamine tartrate (gynergen) [4] is a stable

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1. Lennox, W. G.: The Use of Ergotamine Tartrate in Migraine, New England J. Med. **210**:1061 (May 17) 1934.

2. Spiro, K., and Stoll, A.: Ueber die wirksamen Substanzen des Mutterkorns, Schweiz. med. Wchnschr. **51**:525, 1921.

3. Cohen, M. S., and Githens, T. S.: Pharmacotherapeutics, New York, D. Appleton & Company, 1928.

4. The Sandoz Chemical Works, Inc., supplied the drug used in this investigation.

salt dispensed in ampules suitable for parenteral injection. The intravenous dosage for acute attacks of migraine ranges from 0.5 to 1 cc. (from 0.25 to 0.5 mg.). While ergotamine may produce nausea and vomiting, and occasionally a feeling of constriction in the chest, other untoward results are usually the consequence of excessive dosage.

Ergotamine has been the subject of numerous pharmacologic and physiologic investigations. Dale's [5] comprehensive work in 1906 showed that the intravenous injection of ergot in animals raised their blood pressure, apparently by a peripheral vasoconstrictive action, and reversed the usual pressor effect of epinephrine and that large doses of ergot paralyzed, while small doses stimulated, sympathetic nerve endings. Rothlin [6] demonstrated that ergotamine in large doses exerts a peripheral action as a depressant of the sympathetic innervation and may inhibit or reverse the effect of epinephrine on the blood pressure and heart and that it augments smooth muscle tone, as indicated by experiments on the isolated uterus and intestine. Koppanyi and Evans [7] demonstrated that ergotamine exerts its emetic action through peripheral stimulation of the gastro-intestinal tract. Andrus and Martin [8] conclusively demonstrated in dogs and cats a slowing of the sinus rhythm and of the auriculoventricular conduction time of the denervated heart through depression of the cardiac sympathetic end-organs. Mendez [9] stated the belief that ergotamine depresses the stimulatory but not the inhibitory action of epinephrine. Heymans [10] showed that intravenous administration of ergotamine causes vasoconstriction; Cannon and Bacq [11] demonstrated that ergotoxine prevents the normal manifestations of sympa-

5. Dale, H. H.: On Some Physiological Actions of Ergot, J. Physiol. **34**: 163, 1906.

6. Rothlin, E.: Ueber die pharmakologische und therapeutische Wirkung des Ergotamins auf den Sympathicus, Klin. Wchnschr. **4**:1437, 1925; Contribution à la méthode chimique d'exploration du système sympathique, Rev. neurol. **33**:1108 (June) 1926; Influence de l'ergotamine sur les fonctions sympathiques, Sc. méd., June 15, 1926; The Specific Action of Ergot Alkaloids on the Sympathetic Nervous System, J. Pharmacol. & Exper. Therapy **36**:657, 1929; Zur Pharmakologie des vegetativen Nervensystems, Schweiz. med. Wchnschr. **60**:1001, 1930.

7. Koppanyi, T., and Evans, E. I.: Studies on Emetic and Anti-Emetic Actions of Ergotamine, Proc. Soc. Exper. Biol. & Med. **29**:1181 (June) 1932.

8. Andrus, E. C., and Martin, L. E.: The Action of the Sympathetic on the Excitatory Process in the Mammalian Heart, J. Exper. Med. **45**:1017 (June) 1927.

9. Mendez, R.: Antagonism of Adrenaline by Ergotamine, J. Pharmacol. & Exper. Therap. **32**:451 (April) 1928.

10. Heymans, C.; Bouckaert, J. J., and Morass, A.: Au sujet de l'action vasculaire de l'ergotamine. Inversion de l'action vasoconstrictrice de "vasotonics" du sang défibriné par l'ergotamine, Compt. rend. Soc. de biol. **110**:993, 1932.

11. Cannon, W. B., and Bacq, Z. M.: Hormone Produced by Sympathetic Action on Smooth Muscle, Am. J. Physiol. **96**:392, 1931.

thetic stimulation but does not hinder the liberation of "sympathin" from the stimulated organs. Clark,[12] also working with ergotoxine, found that it may reverse the vasoconstrictive action of epinephrine in the intestines but not in the skin. Woods and the Nelsons [13] corroborated the latter findings with ergotamine. Its effect was more marked in the splanchnic area than in the vessels of the nasal mucosa.

To summarize the physiologic and pharmacologic effects of ergotamine tartrate, it may be said that the drug stimulates smooth muscle, depresses peripheral sympathetic nerve endings, especially those in the splanchnic area and may act as an antagonist of epinephrine. The effect of ergotamine on the sympathetic nervous system has been likened to that of atropine on the parasympathetic system.

One of the theories concerning the etiology of migraine (that of the cerebral vascular spasm) is summarized and discussed by Riley [14] in his excellent review of migraine and by Robey [15] in his treatise on headache. Because it has long been recognized that vasoconstriction may be produced by sympathetic activity, it has been assumed that the spasm of vessels might be relieved by a depressant of sympathetic nerves. This is the explanation advanced by those European writers who have used ergotamine tartrate in the treatment of migraine. If migraine headaches are indeed due to vascular spasm and this spasm is released by ergotamine, there should be changes in the pressure of the blood and of the spinal fluid coincident with the relief of the headache. In this study we have sought for such evidence.

METHOD

Twenty-seven persons were studied, of whom sixteen were women and eleven men. Observations were made on the spinal fluid pressure, on the blood pressure and on the pulse rate before and after the administration of ergotamine tartrate (or saline solution). Eleven subjects were patients who were having an acute attack of headache. The remaining sixteen patients were not subject to attacks and served as a control group. Twelve of these were given ergotamine tartrate; four were given a small intravenous injection of sterile physiologic solution of sodium chloride. A total of thirty-one records was obtained from the twenty-seven patients. On three of the patients who had migraine headaches observations on the pulse rate and blood pressure were made at a time other than that in which the spinal fluid pressure was being recorded. The full observations were not made in every case. Of the thirty-one experiments, the blood pressure was studied in twenty-five, the spinal fluid pressure in twenty-three and the pulse rate in twenty. The detailed observations appear in the accompanying tables.

12. Clark, G. A.: J. Physiol. **80**:429, 1934.

13. Woods, G. G.; Nelson, V. F., and Nelson, E. E.: Effect of Small Amounts of Ergotamine on the Circulatory Response to Epinephrine, J. Pharmacol. & Exper. Therap. **45**:403, 1932.

14. Riley, H. A.: Migraine, Bull. Neurol. Inst. New York **2**:429 (Nov.) 1932.

15. Robey, W. H.: Headache, Philadelphia, J. B. Lippincott Company, 1931.

Records of blood pressure and pulse rate were made at intervals of a few minutes. The spinal fluid pressure was observed continuously in an Ayer spinal fluid manometer with an open end attached to a three way Fremont-Smith lumbar needle by small bore rubber tubing. The entire system of manometer and tubing was first filled with sterile physiologic solution of sodium chloride to atmospheric pressure to avoid loss of spinal fluid into the apparatus. The patient lay on the left side. No record of spinal fluid pressure was made unless there were oscillations of the spinal fluid pressure reflecting the pulse, the respiration and the compression of the abdominal and jugular veins. A short period of hyperpnea (thirty deep breaths), with a consequent temporary lowering of the level of spinal fluid pressure, was often resorted to at the onset of observations in order to ensure a minimum pressure. Readings for spinal fluid pressure were recorded when the pressure had resumed a constant level after completion of the various dynamic tests or of hyperpnea. Throughout each experiment, the highest and lowest pressures for each minute were recorded and subsequently plotted. In all cases, basal levels of spinal fluid pressure, blood pressure and pulse rate were recorded for a period ranging from ten to seventy minutes previous to medication. The total periods of observation varied from one and one-half to three hours and in the cases of migraine included the disappearance time of the headache (with the exception of the two unrelieved patients). The occurrence and time relations of headaches, nausea, vomiting and irregularity in the rhythm of the pulse were noted.

The diagnosis of migraine was made on the history of periodic headaches recurring over a number of years, resistant to therapy and usually but not necessarily associated with nausea, sometimes with vomiting, sometimes with visual disturbances and always with marked general distress or prostration. The family history in all cases suggested a hereditary predisposition. The results of routine examinations of the blood and spinal fluid of the patients were normal.

RESULTS

Clinical Effects.—In addition to the observations listed in tables 1 and 2, the following symptoms were noted: Of the fifteen patients who had migraine, seven experienced nausea and all but one vomited after the administration of ergotamine tartrate. Of the twelve control subjects, one patient had nausea and none had vomiting. As regards the effect of the injection on headache, in the group with migraine, the symptom was completely relieved in twelve of the fifteen experiments. In the control group, transient headache occurred in three of the twelve experiments (table 2; cases 7, 10 and 15).

Cerebrospinal Fluid Pressure.—We have seen a report by only one author who has measured the spinal fluid pressure during an attack of migraine. In five cases Kerppola[16] found pressures of from 80 to 220 mm., with an average of 144 mm. In our nine cases in which readings of spinal fluid pressure were made during headache, the initial readings were 40 to 180 mm., with an average reading of 113 mm. For the group of fourteen patients used as controls, the initial pressures ranged from 95 to 175 mm., with an average of 130. If the two very

16. Kerppola, W.: Ueber die Entstehung und Eiweissbehandlung der Migräne, Monatschr. f. Psychiat. u. Neurol. **61**:83, 1926.

TABLE 1.—*Effect of the Injection of Ergotamine Tartrate on the Pressure of the Spinal Fluid and of the Blood, on the Pulse Rate and on the Symptoms of Patients with Migraine Headache*

Case*	Dose of Ergotamine, Mg.	Spinal Fluid Pressure, Mm. Spinal Fluid: Basal Level	Spinal Fluid Pressure, Mm. Spinal Fluid: Average Change	Radial Pulse Rate, Beats per Min.: Basal Level	Radial Pulse Rate, Beats per Min.: Average Change	Arterial Pressure, Systolic: Basal Level	Arterial Pressure, Systolic: Average Change	Arterial Pressure, Diastolic: Basal Level	Arterial Pressure, Diastolic: Average Change	Time in Minutes for Headache to be: Better	Time in Minutes for Headache to be: Gone	Nausea	Vomiting
1	0.25	40	+30	75	0	120	+ 5	80	0	(Not relieved)		0	0
2a	0.50	110	— 5	...	....	...	....	...	....	(Not relieved)		0	0
2b	0.50	...	....	...	....	130	+15	70	+25	(Not relieved)		+	+
3a	0.50	...	....	...	....	120	+15	90	+10	16	64	+	+
3b	0.12	50	+25	110	— 5	110	+10	80	+10	32	56	+	+
4a	0.50	110	0	...	....	...	....	...	....	20	64	0	0
4b	0.15	...	....	...	....	155	+ 5	100	+10	11	43	0	0
4c	0.50	...	....	...	....	140	+30	90	+45	10	14	+	+
5	0.35	100	+15	...	....	...	....	...	....	30	35	+	0
6	0.50	180	+40	105	—15	140	+20	90	+15	25	30	0	0
7	0.25	145	+20	...	....	...	....	...	....	20	53	0	0
8	0.50	155	+15	110	—45	110	+15	70	+20	13	74	+	+
9	0.50	130	—25	75	— 5	100	+40	70	+10	40	72	+	+
10	0.25	...	....	70	— 5	100	+10	75	0	21	36	0	0
11	0.25	...	....	...	....	115	+ 5	70	+10	27	36	0	0
Average	0.38	113	+13	91	—13	122	+16	80	+14	22	48		

* In cases 4b and 7, 0.12 and 0.25 mg. of ergotamine was given subcutaneously at the same time as the intravenous injection. In cases 8, 10 and 11, 0.25 mg. of ergotamine was given subcutaneously from twelve to sixty minutes after the intravenous injection.

TABLE 2.—*Effect of Intravenous Injection of Saline Solution and of Ergotamine on the Pressure of the Blood and of the Spinal Fluid and on the Pulse Rate of the Control Series of Patients not Subject to Migraine*

Case	Dose of Ergotamine, Mg.	Spinal Fluid Pressure, Mm. Cerebrospinal Fluid: Basal Level	Spinal Fluid Pressure, Mm. Cerebrospinal Fluid: Average Change	Radial Pulse Rate, Beats per Minute: Basal Level	Radial Pulse Rate, Beats per Minute: Average Change	Blood Pressure, Systolic: Basal Level	Blood Pressure, Systolic: Average Change	Blood Pressure, Diastolic: Basal Level	Blood Pressure, Diastolic: Average Change
1	Saline solution	105	0	100	0	105	+ 5	70	+ 5
2	Saline solution	150	0	75	+ 2	140	— 5	80	0
3	Saline solution	175	0	105	— 5	120	— 5	70	+ 5
4	Saline solution	110	0	100	+ 3	105	+ 5	65	+ 5
Average.....		135	0	95	0	118	0	71	+ 4
5	0.35	175	0	105	—20	115	+20	75	+15
6	0.35	160	+50	95	—15	120	+ 5	55	+15
7	0.50	110	+45	100	—15	100	0	55	+10
8	0.50	115	+35	100	0	130	+15	90	+ 5
9	0.50	110	0	85	—20	110	+ 5	75	+10
10	0.30	150	+35	...	....	....	....	...	....
11	0.25	100	+30	75	— 5	120	0	60	+ 5
12	0.50	105	+80	75	—10	125	+45	80	+20
13	0.45	145	+25	90	—10	110	+10	70	+20
14	0.50	95	+10	...	....	...	....	...	....
15	0.50	...	....	110	—35	145	—15	65	+ 5
16	0.50	...	....	75	0	100	+15	70	+15
Average	0.43	127	+31	91	—13	118	+10	70	+12

low readings of 40 and 50 were eliminated from the values for the group with migraine, the average for the two groups would be the same.

As to the effects on the spinal fluid pressure of the injection of ergotamine, the only published observation on man is that made by Urechia.[17] Using the pressure apparatus of Claude, he observed a decrease of tension in eight patients and an increase in two. None of the patients was subject to migraine. The only report dealing with animals is that by Pool,[18] who gave injections to anesthetized cats of from one to ten times the clinical dose of ergotamine tartrate and observed either no change or a rise in the pressure of the spinal fluid.

Turning to the results obtained by us and shown in tables 1 and 2, after the administration of ergotamine the spinal fluid pressure of almost all the patients increased. The abrupt increase of spinal fluid pressure which occurred immediately after injection of ergotamine was undoubtedly due to the pain of the intravenous injection, since it occurred after the injection of saline solution as well as after the injection of ergotamine. After this transient rise, there was a secondary and prolonged rise in the two groups receiving an injection of ergotamine. The pressure remained constant after the first five minutes. As seen in table 1, of the nine patients subject to migraine who were given ergotamine in the midst of headache, only three did not exhibit a rise of spinal fluid pressure. For the other six, the increase in the general spinal fluid level for the period after the injection was from 15 to 40 mm. The average increase in the level of the pressure in the nine cases was 13 mm., or 11 per cent. In the group of ten patients not subject to migraine who were given ergotamine, none experienced a fall of pressure. The greatest rise in this group was 80 mm., the average increase in the pressure level was 31 mm., or 24 per cent (table 2).

In figure 1 is shown the time relation of the average pressure curve. The maximum elevation was reached seven minutes after injection in the group without migraine and sixteen minutes after injection in the group with migraine. The increase in spinal fluid pressure which followed the injection of ergotamine occurred later and was less pronounced in patients during an attack of migraine than in patients not subject to attack.

Blood Pressure.—A number of investigators have reported the effect of ergotamine on the blood pressure of animals. Herrick[19] noted an

17. Urechia, C. I., and Dragomir, L.: L'influence du tartrate d'ergotamine, de l'adrénaline et de l'atropine sur la tension du liquide céphalorachidien, Compt. rend Soc. de biol. **99**:1069, 1928.

18. Pool, J. L., and Nason, G. I.: Cerebral Circulation: XXXV. The Comparative Effect of Ergotamine Tartrate on the Arteries of the Pia, Dura and Skin of Cats, Arch. Neurol. & Psychiat. **33**:276 (Feb.) 1935.

19. Hewes, H. F., and Kendall, A. I.: The Gas Bacillus as an Agent of Intes-Pressure in Femoral Artery of Dog, Proc. Soc. Exper. Biol. & Med. **30**:871, 1933.

increase in the systemic blood pressure of anesthetized dogs, with a concomitant diminution of peripheral (limb) blood flow. Salant, Nadler and Brodman [20] reported an increase in one half and no change in the other half of a series of anesthetized cats. Marinesco [21] noted an increase in pressure after intravenous injection and a decrease after intraventricular administration of ergotamine. In a series of sixty-seven experiments on anesthetized cats given ergotamine tartrate intravenously, Pool [18] obtained an increase of blood pressure in 57 per cent. Rosen-

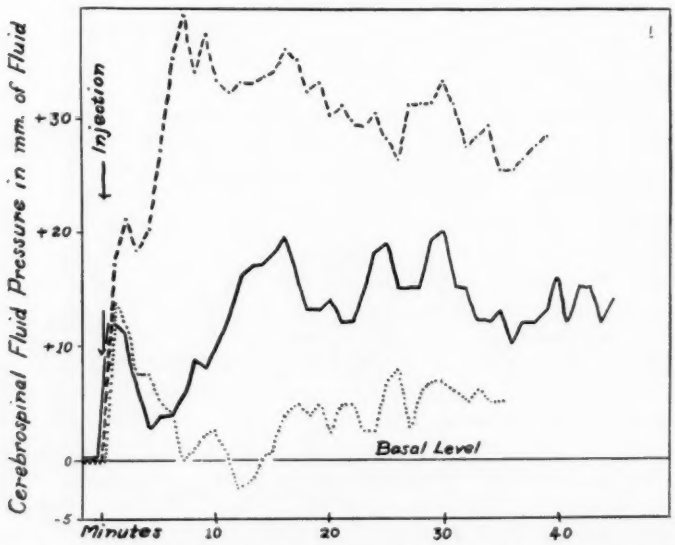

Fig. 1.—Changes in the spinal fluid pressure following the intravenous injection of from 0.25 to 0.5 mg. of ergotamine tartrate. The curves represent the average of the mean readings for the group in question. The basal level is the spinal fluid pressure in the control period before injection. The ordinates represent increase or decrease of pressure (in millimeters of spinal fluid). The abscissas represent minutes of time. In order to represent the average pressure of all cases, the curves could be extended only as far as the shortest period of observation. The curves represent: the nine patients having migraine headache, for whom the average amount of ergotamine injected was 0.38 mg. (solid line); the control group of ten patients not subject to attacks, for whom the average amount injected was 0.4 mg. (broken line); and the control group of four patients not subject to migraine headache, who were given 0.2 cc. of saline solution (dotted line).

20. Salant, W.; Nadler, J. E., and Brodman, K.: Circulatory Reaction to Ergotamine and Effect upon Them Produced by Adrenalectomy and Blood p_H, Proc. Soc. Exper. Biol. & Med. **25**:361 (Feb.) 1928.

21. Marinesco, G.; Soger, O., and Kreindler, A.: Action centrale de l'ergotamine sur la tension artérielle, Compt. rend. Soc. de biol. **107**:191, 1931.

blueth and Cannon [22] expressed the belief that the increase in blood pressure is due to a peripheral effect of the drug and the decrease to a central action. Wright [23] suggested that the rise in pressure may be due to abolition of the carotid sinus reflex. Experiments on animals show, therefore, that the intravenous injection of ergotamine tartrate produces a rise in systolic and diastolic blood pressure. These conclusions cannot be applied unreservedly to man because the animals were in most cases anesthetized and the doses were larger than the amounts used clinically.

Observations on man furnish more conflicting evidence. Barath [24] observed usually a fall in the systolic and a rise in the diastolic pressure. Elevation of the systolic pressure in patients with normal tension was observed by Immerwahr [25] and by Youmans and his associates [26] and in patients with hypertension by Immerwahr.[25] Depression of the systolic pressure was noted in patients with hypertension by Barath [24] and by Meakins and Scriver [27] and in patients with hypotension by Immerwahr.[25] These conflicting reports may be due, as suggested by Youmans and his associates,[26] to the condition of the patient; on the other hand, they may be due to the fact that some patients received the ergotamine intramuscularly or subcutaneously, while others received it by mouth.

Among the twenty-one observations of this study in which the blood pressure was recorded, the intravenous administration of ergotamine tartrate was followed by an increase of the systolic pressure in eighteen instances and by a decrease in one; in two there was no change. The average elevation was 13 mm. of mercury, or 10 per cent. The diastolic pressure increased in nineteen cases and did not change in two. The average diastolic increase was 13 mm., or 17 per cent. Although the average pulse pressure did not change, there were distinct individual variations. The pulse pressure increased in eleven instances, decreased in eight and remained the same in two.

As regards the two groups, the patients with migraine and the controls, all of whom received ergotamine, each of the patients with

22. Rosenblueth, A., and Cannon, W. B.: Some Circulatory Phenomena Disclosed by Ergotamine, Am. J. Physiol. **105**:373, 1933.

23. Wright, S.: Studies of Reflex Activity in Involuntary Nervous System: Action of Ergotamine on Vaso-Motor Reflexes, J. Physiol. **69**:331 (May) 1930.

24. Barath, E.: Untersuchungen über die Ergotaminewirkung bei Menschen mit besonderer Rücksicht auf seine klinischen Anwendungsmöglichkeiten bei inneren Erkrankungen, Ztschr. f. klin. Med. **104**:713, 1926.

25. Immerwahr, P.: Effects of Ergotamine on Pulse, Blood Pressure and Blood Sugar: Comparative Experiments with Atropine, Med. Klin. **23**:1693, 1927.

26. Youmans, J. B.; Trabue, C., and Buvinger, R. S.: Experimental and Clinical Studies of Ergotamine, Ann. Int. Med. **7**:653 (Nov.) 1933.

27. Meakins, J., and Scriver, W. de M.: Treatment [Ergotamine, Acetylcholine, Sodium, Thiocyanate] of Hypertension, Canad. M. A. J. **25**:285 (Sept.) 1931.

migraine had an increase of systolic blood pressure of from 5 to 40 mm., the average increase in the general pressure level being 16 mm., or 12 per cent (table 1). Changes in the control group were more scattered,

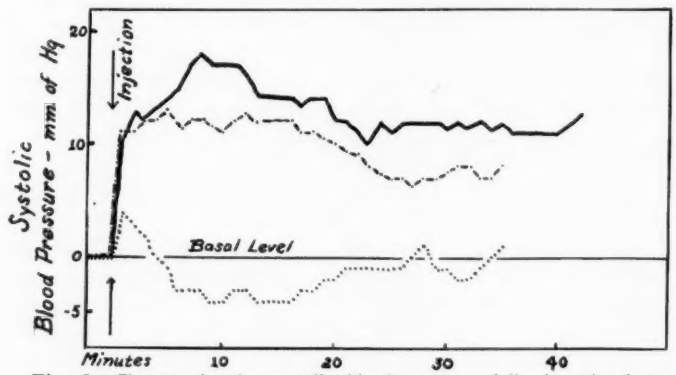

Fig. 2.—Changes in the systolic blood pressure following the intravenous injection of from 0.25 to 0.5 mg. of ergotamine tartrate. The ordinates represent changes of blood pressure in millimeters of mercury; the abscissas, time in minutes. Other explanations are the same as those for figure 1, except that the numbers comprising the three groups are: patients having migraine headache, who were given ergotamine, eleven; patients not subject to attacks, who were given ergotamine, ten; and control patients, who were given saline solution, four.

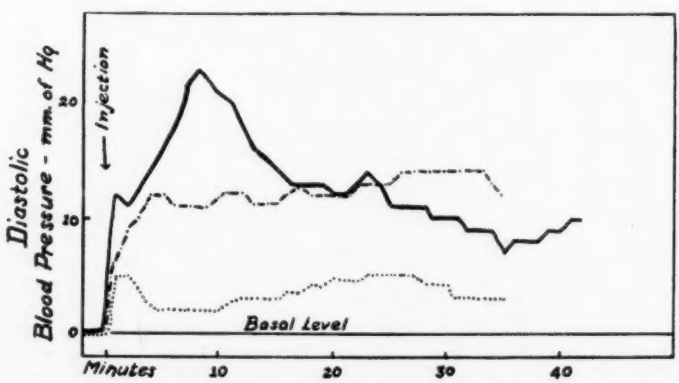

Fig. 3.—Changes in the diastolic blood pressure following the intravenous injection of from 0.25 to 0.5 mg. of ergotamine tartrate. The explanations are the same as in figure 2.

from a decrease of 15 mm. to an increase of 45 mm. The average maximum change was an increase of 10 mm., or 8 per cent (table 2). Inspection of figure 2 shows that the curves for blood pressure (in

contrast with the curves for spinal fluid pressure) had much the same form in the group with migraine as in the control group.

In the case of the diastolic pressure, there was in both groups an average increase which approximated the increase in systolic pressure (tables 1 and 2). The curves, on the basis of time, as shown in figure 3, are, however, different. In the group having migraine headache, there was a sharp increase of diastolic pressure in the first eight minutes after injection. This was perhaps related to the nausea and vomiting which some of the patients experienced in this period.

Heart Rate.—Andrus and Martin [8] demonstrated that ergotamine tartrate slows the cardiac rate of animals, presumably by a depressant action on the cardiac sympathetic end-organs. One of us (Pool [18]) observed that ergotamine given intravenously to anesthetized cats may

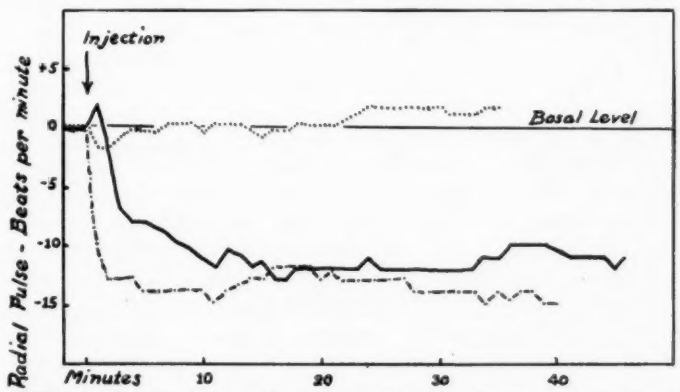

Fig. 4.—Changes in the pulse rate following the intravenous injection of from 0.25 to 0.5 mg. of ergotamine tartrate. The ordinates represent the pulse rate in beats per minute. The abscissas represent minutes of time. The number of patients in the three groups are: patients with migraine headache who were given ergotamine, six; patients in the control group who were given ergotamine, ten; patients in the control group who were given saline solution, four.

produce a marked slowing of the rate, occasionally with irregularity in rhythm.

In man the cardiac rate is also slowed by the administration of ergotamine, as noted by Youmans and his associates,[26] who stated that the effect may be due to vagal excitation, and by Goldman,[28] Porges,[29] Immerwahr,[25] Barath [24] and others. In no report is an elevation of pulse rate mentioned. The evidence presented in our study confirms these observations.

28. Goldman, M.: Recherches cliniques sur l'action de l'ergotamine sur le système végétatif, Arch. d. mal. du cœur **21**:204, 1928.

29. Porges, O.: Treatment of Hyperthyroidism, Med. Klin. **23**:200, 1927.

The injection of ergotamine was followed by bradycardia in thirteen of the sixteen patients whose pulse rate was recorded. The average retardation throughout the postinjection period was from five to forty-five beats per minute. For the sixteen cases, the average decrease was thirteen beats, or 14 per cent. The degree of retardation was very slightly less in the group with migraine (tables 1 and 2). Inspection of figure 4 shows that during the first ten minutes bradycardia was less in the group with migraine. Here again the frequency of vomiting in this group may be explanatory.

COMMENT

What is the significance of the foregoing observations? Can the observed changes in pressure or circulation, consequent to the administration of ergotamine, explain its beneficial effect?

In regard to measurements of intracranial pressure, a finding of subnormal pressure during the attack of migraine would suggest a constriction of the cerebral vascular bed or dehydration of cerebral tissues. In our observations, however, the initial spinal fluid pressure, except in two instances, was not abnormally low, nor did the time of relief from headache in patients coincide with the period of increasing pressure. Furthermore, control patients without headache and patients who were not relieved of headache had as great or a greater rise than patients who were relieved. Two patients who were relieved had a decrease in pressure. These facts permit us to conclude that changes in pressure per se explain neither the presence nor the relief of headache. The observations on pressure do not, however, justify a similar statement concerning a possible generalized vascular spasm. Acute changes in the caliber of cerebral vessels are promptly reflected in increase or decrease of the spinal fluid pressure, but established vascular changes may not be.

If there were spasm of cerebral vessels, the headache might be explained either by a resultant stimulation of sensory nerves or by defective oxygenation or nutrition of tissues. In the latter case, the good effect of ergotamine could be attributed to an improved cerebral blood flow, with flushing away of toxic substances or improvement of the oxygenation of cerebral tissues. Headache is a common symptom of chronic anoxemia. As a matter of fact, Lennox and Gibbs [30] found that ergotamine tartrate does increase the cerebral blood flow in both patients subject to and those not subject to migraine. As in the case of intracranial pressure, the observed improvement in cerebral blood flow cannot be the whole cause of the relief of headache, for other drugs, such as

30. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: The Cerebral Circulation: XXXVI. Effect of Ergotamine Tartrate on the Cerebral Circulation of Man, J. Pharmacol. & Exper. Therap. **53**:113 (Jan.) 1935.

epinephrine, histamine and carbon dioxide (inhaled), which give an even greater increase in flow, do not have the same dramatic effect on headache.

The observed increase in cerebral blood flow after administration of ergotamine is probably secondary to the increase in blood pressure. Neither the increase in blood pressure nor the decrease in pulse rate was significantly different in the patients with migraine and the controls. The only difference which seems important is the relatively small increase in spinal fluid pressure in patients during headache. This cannot be explained by differences in blood pressure, for the group with migraine had a slightly greater increase in blood pressure. Is it possible that the cerebral vessels of patients having headache dilate less readily after injection of ergotamine than the vessels of patients not subject to migraine?

But does ergotamine dilate cerebral vessels? The evidence of increased intracranial pressure is too indirect, for other things might cause the increase. Direct evidence is not supportive. Pool [18] did not obtain a consistent response in pial arterioles of the cat. Nor did Lennox and Gibbs [30] find a sufficient increase in the cerebral blood flow in patients to indicate dilatation of cerebral arterioles. One may conclude that these observations do not indicate that either abnormalities in intracranial pressure (generalized cerebral vascular spasm) or abnormalities in the speed of cerebral blood flow are of specific or exclusive importance in the production or in the relief of migraine headache.

The possibility remains that there may be localized vascular or pressure changes within the cranial cavity which are responsible for pain and which are not reflected in the gross measurements which we have made. Various authors (Hare,[31] Cushing,[32] Dickerson [33] and others) have contended that the pain of migraine arises not from cerebral but from dural arteries. Dickerson secured relief in a small series of cases by ligation of the middle meningeal artery or arteries. Pickering,[34] on the basis of observations of the blood pressure and the spinal fluid pressure after intravenous injection of histamine, stated the belief that the pain of this procedure is due to perivascular edema of dural vessels with pressure on sensory nerves. Most important for our purposes is

31. Hare, F.: The Mechanism of Pain in Migraine, M. Press & Circ. **79**:583, 1905.

32. Cushing, H., in Keen, W. W.: Surgery: Its Principles and Practice, Philadelphia, W. B. Saunders Company, 1908, vol. 3, p. 160.

33. Dickerson, D. G.: Surgical Relief of the Headache of Migraine, J. Nerv. & Ment. Dis. **77**:42, 1933.

34. Pickering, G. W.: Observations on the Mechanism of Headache Produced by Histamine, Clin. Sc. **1**:77 (July) 1933.

the observation made by Pool [35] that in cats dural vessels consistently respond to injection of ergotamine by constriction (as do vessels of the skin), an action dissimilar to that of pial or cerebral vessels. Conceivably, constriction of dilated and engorged dural vessels might explain the relatively small increase in spinal fluid pressure of patients having migraine who are given ergotamine.

In the group of patients whose headaches were relieved by ergotamine, the average period after intravenous injection before relief began was twenty-two minutes, and before the pain disappeared, forty-eight minutes. A glance at the charts will show that the changes in the pressure of the spinal fluid and of the blood and in the pulse rate occurred much more quickly, usually within ten minutes after injection. It seems probable that any explanation of the mechanism of the relief of pain by ergotamine would be a complicated one and include alterations in the vascular bed and blood flow and in dynamics and fluid balance. In this event the few physiologic changes which we have observed would be of contributory importance.

In place of, or in addition to, these considerations, it is possible that ergotamine acts directly as a sedative on the sensory nerves which supply intracranial tissues, particularly those nerves which accompany arteries or supply the dura, or that it acts directly on autonomic nuclei in the hypothalamus. Such a simple explanation does not, however, take into account the fact that ergotamine relieves not only the headache but also other symptoms, such as scotoma, hemianopsia, paralysis and malaise. Obviously the whole problem requires further study.

CONCLUSIONS

With patients subject to migraine and control patients not subject to the disease, observations have been made on the effect of intravenous injection of ergotamine tartrate on the pressure of the spinal fluid and of the blood, on the pulse rate and on the clinical symptoms. In fifteen experiments the patient was in the midst of a migraine headache. In sixteen, the patient was not subject to migraine, and in four of these, saline solution was injected in place of ergotamine.

The average initial spinal fluid pressure during headache was 113 mm., a figure 14 mm. lower than the average pressure for the control group.

Following the injection of ergotamine, there was in both groups a prompt fall in pulse rate and a rise in systolic and diastolic blood pressure and in spinal fluid pressure.

35. Pool, J. L.; Mason, G. I., and Forbes, H. S.: The Cerebral Circulation: XXXIII. The Effect of Nerve Stimulation and Various Drugs on the Vessels of the Dura Mater, Arch. Neurol. & Psychiat. **32**:1202 (Dec.) 1934.

After injection of ergotamine in the patients having headache, the average rise in the level of spinal fluid pressure was 13 mm.; in the controls the level rose 31 mm.

The relief from headache which twelve of the fifteen patients with migraine experienced could not be directly or entirely explained by the observed changes in cerebrospinal fluid pressure or in the circulation. The observations do not lend support to the theory that in migraine headache there is a generalized spasm of cerebral vessels or an abnormality of intracranial pressure.

CHEMICAL STUDIES OF ACUTE POISONING FROM MERCURY BICHLORIDE

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I. ELIMINATION OF MERCURY DURING TREATMENT

The outcome of acute poisoning with mercury bichloride depends chiefly on the amount of mercury absorbed. Prompt emesis is therefore the most efficient treatment.[1] This should be supplemented as soon as possible with copious gastric lavage. Further elimination of the mercury has been sought by repeating the gastric lavage through the subsequent days, by extensive colonic irrigations and by pushing the consumption of fluids to secure diuresis. Local cleansing is a part of the therapeutic intent, but the expected removal of mercury generally has a large share in inciting the prescribing of these measures. As there are apparently no data on how effectively this object is accomplished and on how much mercury is really removed by such treatment, it appeared worth while to undertake these studies. They include the quantitative determination of mercury, by the method described by Booth [2] and ourselves, in the vomitus obtainable, in all the return fluids of gastric lavage and colonic irrigation, in the feces, both those passed in spontaneous stools and after enemas, and in the urine of four patients with acute poisoning from mercury bichloride. The selection proved fortunate, as in two cases the condition was fatal and in the other two it was very mild. The medical service of the university hospitals contributed the material. The patients were brought to the hospital between one-half and one and a half hours after taking from 2 to 25 tablets (0.5 Gm. each) of mercury bichloride, generally in solution. All had vomited before they came to the hospital; in only one case was a specimen of the early vomitus obtained for analysis, and this was incomplete. The quantity of mercury bichloride remaining when the patient came to treatment is therefore unknown. On admission the patients

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were treated according to the usual routine of the hospital. The stomach was washed with several liters of diluted (4 or 5 per cent) solution of sodium bicarbonate; this was repeated at intervals. Vomiting continued more or less in several cases. Copious colonic lavage with physiologic solution of sodium chloride was started on the same day and

TABLE 1.—*Mercury Recovered from Emesis and Gastric Lavage*

	Emesis		Gastric Lavage	
Time	Volume, Cc.	Mercury, Mg.	Volume, Cc.	Mercury, Mg.
W.W.S.: About 9 Gm. of mercury bichloride taken 4/5/32 at 6:00 p.m.				
4/ 5/32 7:00-11:00 p.m.	200	30.36	3,500	35.07
	200	8.8	3,220	21.91
	220	6.4	3,220	0.97
11:00 p.m.	170	0.61	2,500	6.5
Total for the first five hours		46.17		64.45
4/ 6/32 2:00 a.m.	100	0.1	.....	.....
3:00 a.m.	100	0.24	.....	.....
9:00 a.m.	...	....	3,030	0.09
9:00 p.m.	55	0.19	.....	.....
Total for the second day		0.53		0.09
4/ 7/32	100	0.19	2,350	0.19
4/ 8/32	75	0.03	.....	....
Total		46.92		64.73
L.R.O.: About 5.5 Gm. of mercury bichloride taken 3/14/33 at about 9:00 a.m.				
3/14/33 10:00 a.m.	150	159.1	.....	.....
10:15 to 10:45 a.m.	...	.....	2,820	28.48
6:00 p.m.	10	1.36	.....	.....
Total		160.46		28.48
C.B.N.: About 2.5 Gm. of mercury bichloride taken 11/2/32 at 9:15 a.m.				
11/ 2/32 Before lavage	75	39.6	.....	.....
	...	.....	5,500	24.75
2:00 p.m.	...	.....	3,400	1.02
6:00 p.m.	...	.....	3,820	0.23
11/ 3/32 1:00 a.m.	...	.....	3,450	1.82
4:00 p.m.	...	.....	1,700	0.14
Total		39.6		27.96
M.C.N.: About 1 Gm. of mercury bichloride taken 3/7/32 at 10:00 p.m.				
3/ 7/32 10:20 p.m.	...	.....	.....	10.00*
3/ 8/32 7:30 a.m.	80	0.03	.....	.....
3:00 p.m.	...	.....	2,100	0.168
6:30 p.m.	...	.....	2,300	0.046
3/11/32	70	0.0	.....	.....
Total		0.03		10.214*

* Specimen of 180 cc. contained 0.61 mg. of mercury (0.34 mg. per hundred cubic centimeters); assuming that 3 liters was used, the amount recovered equals 10 mg. of mercury.

repeated, generally three times a day, until the end. In the two fatal cases anuria promptly developed, and the patients died after from five to nine days of nephritis and consequent pulmonary edema. Both had severe gastro-enteritis. The patients with mild poisoning did not have oliguria and showed few symptoms after the first day. They were discharged as well on the fifth and eighth day, respectively. Brief accounts of the histories of the individual patients follow. These are arranged in the order of severity of the poisoning. The time and

number of gastric and colonic irrigations are shown with the analytic data in tables 1 and 2. Symptoms and treatments that are not especially relevant to the present inquiry are omitted.

TABLE 2.—*Elimination of Mercury in Stools, Both Spontaneous and After Enemas, and Colonic Irrigations*

		Stools*		Colonic Irrigations	
	Time	Volume, Cc.	Total Amount of Mercury, Mg.	Volume, Cc.	Total Amount of Mercury, Mg.
W.W.S.: About 9 Gm. of mercury bichloride taken 4/5/32 at 6:00 p.m.					
4/ 5/32	Before 11:00 p.m.	800	3.60	3,400	0.48
		270	34.54	4,050	0.77
		285	13.10	.....	....
	11:30 p.m.	600	2.38	.....	....
	Midnight	250	18.2	.....	....
4/ 6/32	2:00 a.m.	75	1.46	.....	....
	4:00 a.m.	200	4.36	.....	....
	8:00 a.m.	...	....	4,960	1.29
	9:45 a.m.	225	0.23	.....	....
	1:00 p.m.	250	0.65	.....	....
	4:00 p.m.	50	1.28	3,470	0.28
	Midnight	...	....	3,150	0.28
4/ 7/32	8:00 a.m.			2,960	0.24
	4:00 p.m.	100	3.02	2,750	0.14
	Midnight			2,500	0.75
4/ 8/32	8:00 a.m.			3,230	0.19
	4:00 p.m.	30	1.34	2,600	0.52
	Midnight			2,875	0.11
4/ 9/32	8:00 a.m.			3,350	0.30
	4:00 p.m.	180	5.44	3,550	0.28
	Midnight			2,500	0.15
4/10/32	8:00 a.m.			3,100	1.8
		50	1.36		
	4:00 p.m.			1,500	1.43
Total			91.0		9.0
L.B.O.: About 5.5 Gm. of mercury bichloride taken 3/14/33 at about 9:00 a.m.					
3/14/33	1:00 p.m.	...	7.9	.....	....
	6:00 p.m.	...	....	6,750	1.35
	7:00 and 9:00 p.m.	10	0.39	.....	....
3/15/33	9:00 a.m.	E 250	0.79	.....	....
	7:00 p.m.	200	2.36	.....	....
3/16/33	9:30 a.m.	E 920	0.65	.....	....
	5:00 p.m.	300	2.22	.....	....
3/17/33	.....	E 740	0.09	.....	....
		1,000	3.55	.....	....
3/18/33	.....	E 1,000	0.09	.....	....
		2,000	2.05	.....	....
3/19/33	.....	E 450	0.16	.....	....
		400	0.39	.....	....
3/20/33	.....	E 800	1.06	.....	....
		650	1.35	.....	....
3/21/34	.....	E 100	0.04	.....	....
		150	0.34	.....	....
3/22/23	.....	E 200	0.06	.....	....
Total			23.5		1.4
C.B.N.: About 2.5 Gm. of mercury bichloride taken 11/2/32 at 9:15 a.m.					
11/ 2/32	.....	300	0.45	3,850	1.73
		225	3.80	3,850	0.73
		300	0.82	3,850	0.81
11/ 3/32	9:00 a.m.	...	....	7,450	0.30
	4:00 p.m.	...	....	4,300	0.25
	7:00 p.m.	300	0.18	.....	....
11/ 4/32	11:30 a.m.	...	....	7,450	0.15
	4:00 a.m.	...	.....	7,400	0.15
Total			5.25		4.12

* E indicates enema.

TABLE 2.—*Elimination of Mercury in Stools, Both Spontaneous and After Enemas, and Colonic Irrigations—Continued*

Time	Stools*		Colonic Irrigations	
	Volume, Cc.	Total Amount of Mercury, Mg.	Volume, Cc.	Total Amount of Mercury, Mg.
M.C.N.: About 1 Gm. of mercury bichloride taken 3/7/32 at 10:00 p.m.				
3/ 8/32 Midnight	E 930	1.42	.....	....
2:30 a.m.	E 1,030	2.96	.....	....
3:00 a.m.	...	....	4,440	1.73
7:00 a.m.	...	....	5,620	0.17
2:00 p.m.	...	....	3,000	0.06
7:00 p.m.	75	1.72	.....	....
3/ 9/32 8:00 a.m.	1,500	1.35	3,820	0.11
4:00 p.m.	...	....	3,770	0.11
6:00 p.m.	110	0.14	.....	....
3/10/32 8:00 a.m.	...	....	5,220	0.0
4:00 p.m.	...	....	5,600	0.05
3/11/32 8:00 a.m.	...	....	6,000	0.12
4:00 p.m.	...	....	5,800	0.06
3/12/32 8:00 a.m.	...	....	5,800	0.12
4:00 p.m.	...	....	5,800	0.64
Total		7.59	Mixed with feces	3.17

REPORT OF CASES

CASE 1.—On April 5, 1932, about 6 p. m., W. W. S., a Negress aged 25, dissolved 25 tablets (0.5 Gm. each) of mercury bichloride in water and drank between a half and the whole of this (about 9 Gm. of mercury bichloride) according to varying reports. The patient had not taken any food for the preceding eight hours. She vomited within three or four minutes and was treated in twenty minutes with apomorphine hydrochloride, 1/10 grain (6.4 mg.) hypodermically, and with the whites of three eggs in a quart (946 cc.) of milk. Almost continuous vomiting set in within a few minutes. The patient was admitted to the emergency ward at 7 p. m. and was given gastric lavage and treated for shock. She vomited repeatedly during the remainder of the first day and several times on the second and third days. The stools were bloody. Gastric lavage with 3 or 4 liters of solution of sodium bicarbonate was given at intervals during three days. Colonic irrigations with 0.8 per cent solution of sodium bicarbonate were given three times a day until death. Anuria persisted throughout. Death from respiratory failure occurred on the fifth day. Permission for autopsy was refused.

CASE 2.—On March 14, 1933, about 9 a. m., L. R. O., a white man 49 years old, swallowed 11 (0.5 Gm. each) tablets of mercury bichloride. He vomited before admission (accounts were discordant as to amount and time). Part of the vomitus expelled at 10 a. m. was analyzed. The patient was admitted to the emergency ward at 10:15. The stomach was lavaged with 5 per cent solution of sodium bicarbonate. He vomited repeatedly on the first day, but only partial specimens were analyzed. Bloody diarrhea developed several hours after his admission. Colonic irrigations with 7 liters of physiologic solution of sodium chloride were given at 6 p. m. on the first day, and enemas were administered daily until death. Complete anuria continued from 5 p. m. of the first day until the fifth day; then oliguria persisted until death (catheterization gave 50 cc. of fluid on the sixth day, 180 cc. on the seventh day and 270 cc. on the eighth day). Marked edema and anasarca developed, and the patient died of pulmonary edema. Autopsy showed gastro-enteritis, colitis and nephritis.

CASE 3.—On Nov. 2, 1932, about 9:15 a. m., C. B. N., a Negress 32 years old, swallowed 5 tablets (0.5 Gm. each) of mercury bichloride (total dose, 2.5 Gm.)

in coffee. She vomited in ten or fifteen minutes and was admitted to the emergency ward at 9:45 a. m. Gastric lavage with 6 liters of solution of sodium bicarbonate was administered. Further lavage was given at 2 and at 6 p. m. on this day and twice on the next day. Repeated colonic irrigations were administered. Polyuria occurred from forced intake of fluids. The patient felt well on the next day.

CASE 4.—On March 7, 1932, at about 9:55 p. m., M. C. N., a white woman aged 40, swallowed 2 tablets (0.5 Gm. each) of mercury bichloride (total dose, 1 Gm.). She vomited in five and ten minutes; the specimens were not analyzed. She was admitted to the emergency ward between 10:20 and 10:35 p. m. Gastric lavage was given and repeated twice on the next day. Only part of the material recovered was saved for analysis. Colonic irrigation with solution of sodium bicarbonate was given three times on the first day and twice daily until the patient was discharged. The volume of urine was above normal throughout.

QUANTITATIVE DATA ON THE ELIMINATION OF MERCURY

In view of the paucity or absence of published data on the removal of mercury by lavage in cases of acute mercury poisoning, it seems advisable to record the results of analysis rather fully.

Emesis After Patients Came Under Observation.—All the patients reported on here had vomited before they came to the hospital. There is little information as to how much mercury bichloride was lost this way, but presumably it was the greater part of the amount taken. In one case (that of L. R. O.) a specimen was preserved, and this fraction contained 159 mg. of mercury, about 3.7 per cent of the amount taken. After the patient's admission the mercury eliminated by emesis was insignificant in all instances, namely, 46.2, 1.36, 39.6 and 0.03 mg. of mercury, equivalent to 0.7, 0.03, 2.1 and 0.004 per cent of the amount taken.[3] Practically all of this was found in the first vomitus after admission, as shown in table 1. Prolongation of emesis is therefore of no value for the elimination of mercury.

Gastric Lavage.—Promptly after admission, i. e., in from one-half to one and a half hours after the poison was swallowed, the stomach was washed with from 3 to 5 liters of 4 to 5 per cent solution of sodium bicarbonate, and the lavage was usually repeated several times in the first day; in one case it was repeated at varying periods on two subsequent days, as shown in table 1. The total amount of mercury removed by lavage amounted to 64.7, 28.5, 28 and 10.2 mg. of mercury, equivalent to 0.95, 0.7, 1.51 and 1.37 per cent of the amount taken. These quantities are also rather insignificant. Practically all the mercury that was obtainable by gastric lavage was secured in the first washing in the emergency room, the later washings in the ward containing only

3. The cases are always arranged in order of decreasing severity: 1 to 4; W.W.S., L.R.O., C.B.N. and M.C.N.

0.75, 3.21 and 0.21 mg. The first gastric lavage is of course imperative; the later repetitions appear to be of little value for the removal of mercury.

Elimination Through Intestines.—The stools and material recovered after irrigations of the colon would contain any mercury which had escaped absorption after passing the pylorus and mercury which had been excreted with the bile and through the intestines. The presence of severe colitis has perhaps helped to give the impression that these quantities would be considerable, so that they would be toxic locally and perhaps systemically by reabsorption. This is partly responsible for the emphasis on colonic irrigation. The facts as shown in table 2 are instructive. The total amount of mercury which passed through the rectum during the entire stay of the patients in the hospital was as follows (in milligrams):

	Case			
	1	2	3	4
Stools, spontaneous and after enemas	90.94	23.49	5.25	7.59
Colonic irrigations	9.01	1.35	4.12	3.17
Totals	99.95	24.84	9.37	10.76
Percentage of dose	0.65	0.61	0.50	1.45
Days	5	9	3	5

The absolute amount as well as the percentage is surprisingly small; so evidently the mercury that passes from the stomach into the intestine is effectively absorbed and little is reexcreted by this channel. This excretion is not increased by colonic irrigations, which in the whole period generally contained less than 4 and never more than 9 mg. of mercury. The irrigations may be useful in combating colitis but not for the removal of mercury. The elimination of mercury from the intestines is greatest on the first day; it falls to from one third to one twelfth on the second day and then runs an irregular course, about one half of the level of the second day being eliminated each day for the remainder of the period of observation, averaging as follows:

Patient	Time	Average Intestinal Elimination of Mercury per Day (Mg.)
W.W.S.	Third to fifth day	4.30
L.R.O.	Third to ninth day	1.72
C.B.N.	Third day	0.30
M.C.N.	Third to fifth day	0.33

The late elimination from the intestines, therefore, varies with the dose. It probably represents excreted rather than unabsorbed mercury.

Urine.—This is shown in table 3. The most severely poisoned patient, W. W. S., was anuric throughout; consequently there was no urinary excretion of mercury. The other fatally poisoned patient eliminated nearly 10 mg. of mercury in the first eight hours, a high level for the urine but a very small amount in relation to the dose. This patient then became anuric. In the fatal cases, therefore, little or no mercury was eliminated in the urine. The two mildly poisoned patients

had marked polyuria, due to forcing of the intake of fluids and perhaps also to the diuretic effect of the smaller doses of mercury. Notwithstanding the polyuria, the kidneys excreted only small quantities of mercury, totaling 1.5 and 2.3 mg. in the five days and averaging from 0.3 to 0.5 mg. per day. Even on the first day, the excretion was only 1 and 1.7 mg. The excretion of mercury in the urine, therefore, seems insignificant in acute mercuric poisoning, even when the patient is polyuric.

TABLE 3.—*Elimination of Mercury in the Urine*

	Volume of Urine, Cc.	Total Amount of Mercury, Mg.
W.W.S.: About 9 Gm. of mercury bichloride taken 4/5/32 at 6:00 p.m.; anuria until death on the fifth day		
L.R.O.: About 5.5 Gm. of mercury bichloride taken 3/14/33 at 9 a.m.		
First eight hours	600	9.7
Anuria until the sixth day; then small quantities by catheter (50 cc. on sixth day; 180 cc. on seventh day; 270 cc. on eighth day); mercury not reported, but amount would have been insignificant		
C.B.N.: About 2.5 Gm. of mercury bichloride taken 11/2/32, 9:15 a.m.		
11/ 2/32 11:30 a.m. (on admission)	250	0.58
4:00 p.m.	200	0.21
6:00 p.m.	350	0.04
6:00 p.m. to 11:00 p.m.	450	0.08
11:00 p.m. to 7:00 a.m.	1,600	0.06
Total for 32 hours		0.97
11/3 to 11/4, 7:00 a.m. to 7:00 a.m.	6,640	0.27
11/4 to 11/5, 7:00 a.m. to 7:00 a.m.	5,350	0.05
11/5 to 11/6, 7:00 a.m. to 7:00 a.m.	3,600	0.11
11/6 to 11/7, 7:00 a.m. to 7:00 a.m.	1,900	0.10
Total in five days		1.5
M.C.N.: 1 Gm. of mercury bichloride taken 3/7/32, 9:55 p.m.		
3/ 8/32 7:00 a.m.	170	0.74
11:00 a.m.	290	0.41
1:45 p.m.	720	0.49
7:00 p.m.	900	0.07
Total for nineteen hours		1.71
3/ 9 to 3/10, 7:00 a.m. to 7:00 a.m.	2,110	0.21
3/10 to 3/11, 7:00 a.m. to 7:00 a.m.	1,860	0.13
3/11 to 3/12, 7:00 a.m. to 7:00 a.m.	1,400	0.13
3/12 to 3/13, 7:00 a.m. to 7:00 a.m.	800	0.12
Total for five days		2.30

Summary.—The relative rôle of the various channels of elimination and treatments is shown in table 4. The first two divisions give the amounts eliminated during the whole sojourn in the hospital. Emesis was not included since complete data were not available. It is seen that the total quantities of mercury removed by gastric and colonic lavage in the stools and in the urine during this entire period are only from 0.5 to 3 per cent of the total amounts. The actual amounts ranged from 23 to 164 mg. of mercury. The fatal dose of absorbed mercury

bichloride is not known. If in analogy to experiments on animals 5 mg. per kilogram is taken as a fair approximation, this would amount to 300 mg. of mercury per person. On this basis, the amount eliminated, except for emesis, would represent from one tenth to one half of the fatal dose. Practically all of this was in the gastric lavage of the first day and in the feces. Copious, prolonged colonic irrigations removed in all instances from one two hundredths to one thirty fifth of this assumed fatal dose, and up to one thirtieth of the dose was excreted in the urine.

TABLE 4.—*Total Amount of Mercury Removed*

Patients		W.W.S.	L.R.O.	C.B.N.	M.C.N.
Dose of mercury bichloride		9.0 Gm.	5.5 Gm.	2.5 Gm.	1.0 Gm.
Mercury equivalent		6.6 Gm.	4.06 Gm.	1.85 Gm.	0.74 Gm.
Milligrams of mercury recovered	Gastric lavage	64.7	28.5	28.0	10.2
	Feces, spontaneous and after enemas	91.0	23.5	5.25	7.59
	Colonic irrigations	9.0	1.4	4.12	3.17
	Urine	0.0	9.7	1.5	2.3
	Total	164.7	63.1	38.9	23.26
Percentage of amount taken	Gastric lavage	0.98	0.70	1.51	1.37
	Feces, spontaneous and after enemas	1.38	0.58	0.28	1.02
	Colonic irrigations	0.13	0.034	0.22	0.42
	Urine	0.0	0.23	0.08	0.31
	Total	2.49	1.54	2.09	3.12
Mercury (Mg.) removed by:		From 6 Hours to 6 Days	From 12 Hours to 9 Days	From 15 Hours to 5 Days	From 22 Hours to 6 Days
	Emesis	0.75	0.0	0.0	0.0
	Gastric lavage	0.28	...	1.96	....
	Feces, spontaneous and after enemas	19.14	15.20	0.18	1.98
	Colonic irrigations	7.75	...	0.85	0.60
	Urine	....	...	0.59	0.59
	Total	27.92	15.20	3.58	3.17

CONCENTRATION OF MERCURY IN EXCRETA

The concentration of mercury in the vomitus, stools and urine helps to decide whether the mercury in the digestive tract is unabsorbed or excreted and also throws light on the possibility of local injury by the excretion of mercury. The concentration in the specimens of vomitus and feces is cited only when there was no gastric lavage or colonic irrigation, respectively, for several hours preceding the collection. The data are shown in table 5. The concentrations always refer to milligrams per hundred cubic centimeters or parts per hundred thousand.

Vomitus.—The two highest concentrations, 53 and 106 mg. of mercury per hundred cubic centimeters, are for emesis within the first hour, before lavage. One patient, L. R. O., who was given relatively little lavage still yielded 13.6 mg. per hundred cubic centimeters at the

end of nine hours. All the others yielded less than 1 mg. per hundred cubic centimeters, ranging from 0.04 to 0.34 mg., between eight and twenty-seven hours; and the averge concentration was 0.19 mg. on the second day and 0.04 mg. on the third day. The low concentration suggests that this represents excreted rather than unabsorbed mercury.

Feces.—The concentration in the stools was distinctly higher than that in the late samples of vomitus but naturally lower than in the early

TABLE 5.—*Concentration of Mercury (Milligrams per Hundred Cubic Centimeters) in the Excreta*

		Vomitus		Stools		Urine	
Patient	Dose of Mercury Bichloride	Time*	Concentration	Time	Concentration	Time	Concentration
W.W.S.	9 Gm.	8 hours.....	0.10	First 12 hours..	0.4 to 12.8; median 2.9	Anuria	
		9 hours.....	0.24				
		27 hours.....	0.34				
		2nd day.....	0.19	2nd day.....	0.28 to 3.02		
		3rd day.....	0.04	3rd day.....	4.50		
				4th day.....	3.00		
				5th day.....	2.72		
L.R.O.	5.5 Gm.	1 hour.....	106.0†	Diarrhea			
		9 hours.....	13.6	12 hours.....	3.90	8 hours.....	1.620
				2nd day.....	1.20	Anuria after eight hours	
				3rd day.....	0.74		
				4th day.....	0.36		
				5th day.....	0.11		
				6th day.....	0.10		
				7th day.....	0.20		
				8th day.....	0.23		
C.B.N.	2.5 Gm.	½ hour.....	53.2†	1st day.....	0.15	2 hours.....	0.230
					1.70	7 hours.....	0.110
					0.27	9 hours.....	0.010
				2nd day.....	0.06	14 hours.....	0.020
						22 hours.....	0.004
						2nd day.....	0.004
						3rd day.....	0.001
						4th day.....	0.003
						5th day.....	0.005
M.C.N.	1 Gm.	10 hours.....	0.04	21 hours.....	2.30	9 hours.....	0.450
				2nd day.....	0.09	13 hours.....	0.140
					0.13	16 hours.....	0.070
						21 hours.....	0.008
						2nd day.....	0.010
						3rd day.....	0.007
						4th day.....	0.009
						5th day.....	0.015

* The time is that which elapsed after the taking of the poison.
† Concentration of mercury before first lavage.

samples. The highest concentration of mercury in the stools was for the most severely poisoned patient, W. W. S.; it reached 12.8 mg. per hundred cubic centimeters on the first day and ranged between 2.7 and 4.5 mg. on the last three days before death. The failure of the concentration to decline after the first day indicates the presence of excreted rather than unabsorbed mercury. The other fatally poisoned patient, L. R. O., had diarrhea until death, and the fecal concentration of mercury was accordingly lower, progressing from 3.9 mg. per hundred cubic centimeters on the first day to 0.36 mg. on the fourth day. From then until death, on the eighth day, it oscillated between 0.1 and 0.23 mg.

This continued level presumably represents excretion. The two patients with mild poisoning attained values of only 1.7 and 2.3 mg. of mercury per hundred cubic centimeters on the first day, and the amounts fell to 0.06, 0.09 and 0.13 mg. on the second day. It appears from the persistence of the concentration in late specimens that the amount of mercury in the feces after the second or third day represents excreted rather than unabsorbed mercury. The level maintained in the case of most severe poisoning, from 2 to 4 mg. per hundred cubic centimeters, could be conceived as injurious. The values in the other cases, from 0.15 to 0.23 mg., fall within the range of values for the concentration in urine found in cases in which mercury has been administered therapeutically and would therefore probably not be locally injurious.

Urine.—The concentration of mercury in the urine could not be estimated in the fatal cases because of anuria. In the cases of mild poisoning it is very low (partly because of polyuria), 0.27 and 0.45 mg. per hundred cubic centimeters even on the first day and only from 0.001 to 0.015 mg. after the first day. These concentrations are lower than those often found in patients given mercurial therapy and are therefore not injurious to the urinary organs. The concentration found in the early samples of urine of the fatally poisoned patient, L. R. O., 1.62 mg. per hundred cubic centimeters, would presumably be injurious.

Summary.—For the three excreta the range and the median of the concentrations for all the patients are (mg. per hundred cubic centimeters):

	Range	Median
Vomitus	0.03 to 106.1	0.24
Feces	0.06 to 12.8	0.74
Urine	0.001 to 1.62	0.01

For the individual patients, the medians (exclusive of the early samples of vomitus of L. R. O.) are:

Patient	Vomitus	Feces	Urine
W.W.S.	0.19	2.6	.....
L.R.O.	13.6	0.30	.....
C.B.N.	.....	0.21	0.005
M.C.N.	.....	0.13	0.012

It is seen that the concentration in the feces was from eleven to forty times that in the urine for C. B. N. and M. C. N. and fourteen times higher than that in the vomitus for W. W. S. The vomitus of L. R. O. alone had a higher concentration than the feces, but it evidently represented unabsorbed, not excreted, mercury. It appears, then, that mercury is eliminated in considerably higher concentration from the intestinal tract than from the stomach or in the urine. Very likely the relatively high intestinal concentration occurs in the bile, although the

excretion of granular mercurial compounds by the intestinal lymphocytes may play a part.

SUMMARY AND CONCLUSIONS

The elimination of mercury was studied in four cases of acute corrosive poisoning from mercury bichloride, two fatal and two mild, in which the patients were treated by copious gastric lavage and colonic irrigations.

Only the early emesis removed considerable quantities of mercury. The total amount removed by gastric lavage and colonic irrigations and in the stools and urine amounted to only from 23 to 164 mg. of mercury, representing from 1.5 to 3.25 per cent of the mercury taken. Initial gastric lavage is imperative, but later repetition is superfluous. Colonic irrigations removed only insignificant quantities, from 1.4 to 9 mg. of mercury. The urinary elimination was also almost negligible; in the cases of severe poisoning there was anuria. In those of mild poisoning there was polyuria but the total urinary excretion of mercury in five days was only 1.5 and 2.3 mg.

The concentration of mercury after the first, second or third day ran practically level in the vomitus, feces and urine, indicating that the mercury in the stomach and intestines at this time is being excreted. The concentration was ten times higher or more in the feces than in the urine or the late vomitus. In general, the concentrations, even in the feces, were within the limits of the concentration found in the urine in cases of the therapeutic use of mercury and would therefore not be materially irritant. The fecal concentration in the case of most severe poisoning possibly exceeded this level.

II. DISTRIBUTION OF MERCURY IN THREE PATIENTS WHO CAME TO AUTOPSY

Notwithstanding the frequency of poisoning from mercury bichloride, very few determinations of mercury in cases of this condition are on record. Lomholt,[4] in an exhaustive review, cited two series. The larger of these, that of Ludwig and Zillner, which included eight cases of mercuric poisoning, six of which were from mercury bichloride, dates from 1890, and an unsatisfactory method was used (*mit einer recht unvolkommenen analytischen Methode*—Lomholt). This leaves only Lomholt's own series of four cases, two being instances of acute poisoning with mercury bichloride and two, of chronic poisoning by inunctions. Somewhat more numerous studies have been made on animals,

4. Lomholt, Svend: Quecksilber, Theoritisches, Chemisches und Experimentelles, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 18.

a good part also with unsatisfactory methods. Lomholt pointed out that the values obtained in these various series agree sufficiently in their general features to permit general conclusions. However, the quantities are not properly comparable, so that reliable data exist at present for only two clinical cases of poisoning with mercury bichloride. A search of the "Quarterly Cumulative Index Medicus" and of *Chemical Abstracts* failed to locate any later analyses. It seems most desirable to enlarge this number. Through the cooperation of the departments of medicine and pathology at the hospitals of the university, opportunity was given to study three cases of the usual type, ending fatally in from six to nine days. One of these cases (that of L. R. O.) was included in the studies on excretion reported in the first part of this paper. The analyses were restricted chiefly to the organs concerned with excretion and included the excreta, when obtainable, and the blood.

The case reports are abstracted briefly, so far as they bear especially on the present study. It may be premised that all the patients were treated with gastric lavage, generally with colonic irrigations and with injections of saline solution, according to indications. Anuria and fatal uremia developed in all patients.

REPORT OF CASES

CASE 1.—L. R. O., a white man aged 49, took about 5.5 Gm. of mercury bichloride. He vomited within an hour (discordant accounts as to time and number of emeses). Gastric lavage was started in one and a quarter hours. There was complete anuria from the sixth hour to the fifth day; then oliguria persisted until death occurred, on the ninth day. This patient was also studied for elimination of mercury. The total amount of mercury (in milligrams) recovered was: in vomitus (specimens), 160.5; by gastric lavage, 28.5; in feces, passed in spontaneous stools and after enemas, 23.5; by colonic irrigations, 1.4, and in the urine, 9.7.

CASE 2.—J. T. N., a white man aged 41, took 2.5 Gm. of mercury bichloride. The patient vomited repeatedly within twenty minutes. Gastric lavage was started within half an hour. There was scanty bloody urine on the first day; then the patient became anuric. There was bloody diarrhea. Uremic coma took place on the sixth day, and death occurred.

CASE 3.—W. M. T., a white man aged 28, took 1 Gm. (or more) of mercury bichloride. He vomited within twenty minutes. Gastric lavage was administered within half an hour. Hematuria occurred within an hour. Oliguria developed, with 350 cc. of urine on the second day and 70 cc. on the fourth day. Death occurred on the eighth day.

The histories of the three cases are closely similar. They differ chiefly in the dosage of mercury bichloride (5.5, 2.5 and 1 Gm.), and this may have been varied by the amount of vomiting. All the patients died between the sixth and the ninth day. It will be shown that the mercury content of the organs was strikingly similar for two patients, J. T. N. and L. R. O. For W. M. T. it was about a third of

that of the other two. Considering both the duration of life and the mercury content, the ranking of the patients according to the severity of the poisoning would appear to be J. T. N.>L. R. O.>W. M. T. However, the results are sufficiently related to justify averages.

CONCENTRATION OF MERCURY

Organs.—The concentration is shown comprehensively in table 6 for our three patients and for Lomholt's patients, individually and as averages; the median for the seven patients of both series (obtained by averaging the three or four central values) and the average for the eight patients of the Ludwig and Zillner series are given. The data for Lomholt's patients and ours agree so closely that averages are justified. The Ludwig and Zillner data show the same sequence, but they run distinctly higher than the others, presumably owing to the analytic method. They cannot, therefore, be averaged with the data for Lomholt's patients, but they appear consistent in themselves and support the general conclusions. The greatest divergence in concentrations is in the intestines, probably owing to unabsorbed mercury. The use of copious colonic irrigation seems to make our series the more reliable in this respect.

One of the most impressive features of the table is the surprisingly close quantitative agreement among the individual values for the seven patients of Lomholt's series and ours, notwithstanding the differences in the histories as to dose and length of time which elapsed before treatment. However, the dosage has a distinct effect, as reflected in the lower concentration of mercury found in case 3 (dose, 1 Gm.) as compared with that found in cases 1 and 2 (doses, 5.5 and 2.5 Gm., respectively) and that in Lomholt's case 4, in which the patient died in six days, as compared with that in his case 2, in which the patient died in three days and therefore presumably absorbed a larger quantity. On the other hand, two of his patients (cases 1 and 3), who died after several months of treatment with inunctions and who had an absolutely different history, showed concentrations intermediate between those for the two patients with acute poisoning observed by him in every organ except the intestines, in which the quantities appear high owing to the presence of unabsorbed mercury.

As for the individual organs, the kidneys invariably have the highest concentration. This holds also for the individual patients in the Ludwig and Zillner series and for all the animal series. The concentration in the liver ranks next. The other organs follow at a considerable distance. Taking the concentration in the kidneys as a measure of comparison for the combined figures on the seven patients observed by Lomholt and us and arranging the other solid organs in order of descending concentrations, the liver averages about one-half to two-thirds the con-

TABLE 6.—*Concentration of Mercury in Human Beings with Mercury Poisoning* *

	Investigators										
	Sollmann and Schreiber				Lomholt				Average of the Four (L)	Combined,‡ Median of Seven	Ludwig and Zillner, Median of Eight
	Patient J.T.N.	Patient L.R.O.	Patient W.M.T.	Average	Patient II	Patient IV	Patient I	Patient III			
Mercury compound	Mercury bichloride	Mercury bichloride	Mercury bichloride		Mercury bichloride	Mercury bichloride	Mercury benzoate inunctions	Inunction			
Dosage of mercuric chloride, Gm.	2.5	5.5	1	3	....	....	....	....	....	....	....
Days before death	6	9	8	8	3	6	37	77	....	....	....
Kidneys	3.50	3.32	2.38	3.07	7.0	1.60	6.31	3.39	4.54	3.79	8.12
Liver	2.50	2.58	1.04	2.04	3.21	0.32	1.20	2.45	1.80	2.05	4.65
Spleen	....	....	....	....	1.0	0.43	0.6	0.15	0.55	0.55	0.66
Colon	0.51	0.283—	0.30	0.36	(4.98?)	0.86	0.46	0.20	0.51	0.49	1.85
Ileum	0.41	0.21	0.20	0.27	0.85	0.37	0.64	0.21	0.51	0.43	15.19
Duodenum	0.22	0.54	0.06	0.27	....	....	....	....	....	0.27	....
Heart	....	....	....	....	0.30	0.24	0.37	0.30	0.30	0.30	0.12
Skeletal muscle	....	....	....	....	....	....	0.25	....	0.25	0.25	0.07
Lung	....	....	....	....	0.57	0.03	0.1	0.1	0.20	0.20	0.28
Brain	....	....	....	....	0.17	0.10	0.15—	....	0.14	0.14	0.08
Feces, last day	W.W.S.† 2.72	0.23	....	1.48	....	....	....	....	....	....	....
Bile	....	1.22	0.10	0.66	....	....	....	....	....	0.66	1.5
Blood	0.10	0.12	0.015	0.08	....	....	....	....	....	0.08	....
Peritoneal fluid	....	0.026	....	0.026	....	....	....	....	....	....	....
Urine from the bladder	....	0.013	....	0.013	....	....	....	....	....	....	....

* The concentration in the organ is expressed in milligrams per hundred grams moist weight; that in the fluids, in milligrams per hundred cubic centimeters.

† Fatal case described in paper I.

‡ Lomholt, Schreiber and Sollmann.

centration in the kidneys; the spleen, one-seventh; the intestines, one-ninth (there being no constant difference in the various levels); the heart, skeletal muscle and lung, about one-fifteenth, and finally the brain, about one twenty-seventh. In a single analysis made by Ludwig and Zillner bone ranks somewhat lower than spleen.

Blood.—The concentration in the blood was 0.10, 0.12 and 0.015 mg. per hundred cubic centimeters for our three patients (cases 1 to 3, respectively). The first two values represent about one thirtieth, and the last represents only about one one hundred and seventieth, of the concentration in the kidneys. The average in the blood of the three patients is 0.08 mg., about one fortieth of the concentration in the kidneys. The other series do not contain any analyses of the blood, but in fourteen patients undergoing energetic treatment with inunctions Lomholt found a range of from 0.04 to 0.33 per hundred cubic centimeters, with a median of 0.11 mg. This is just about the same as for our fatal series, showing that the concentration of mercury in the blood has fallen to an innocuous level before death. This would be expected from the general knowledge of the rapid rate with which extraneous dissolved substances leave the blood stream. The direct injury from mercury from which the patient dies on the ninth day is probably completed within one or two hours after the poison is swallowed, the further course consisting essentially of the secondary consequences of the early injury.

Comparison of the concentration in the blood and that in other fluids is instructive. It may first be noted that Lomholt found that in three patients the concentration of mercury in the blood serum and that in the corpuscles was practically the same; so the concentration in the whole blood may be taken also as that of the serum.

Ascitic Fluid.—In the peritoneal fluid L. R. O. (case 1) showed a very low concentration of mercury, 0.026 mg. per hundred cubic centimeters, a fourth or fifth of the level for blood. Lomholt found the concentration of mercury in the ascitic fluid of three patients treated with inunctions to be from 0.02 to 0.06 mg., and therefore lower than that of the blood (from 0.04 to 0.33 mg).

Urine.—For L. R. O. (case 1) the concentration in the bladder urine at autopsy was 0.013 mg. per hundred cubic centimeters, only a tenth that of the blood. The daily output of urine was very small. In Lomholt's series of patients treated with inunctions, the concentration of mercury in the urine (0.065 to 0.35 mg. per hundred cubic centimeters) was generally higher than that in the blood for the same fourteen patients, but the difference in the medians was not great (urine, 0.163 mg.; blood, 0.11 mg.).

Bile.—The concentration of mercury in the bile removed from the gallbladder at autopsy was 1.22 mg. per hundred cubic centimeters in

the case of more severe poisoning (L. O. R.) and 0.10 in the case of milder poisoning (W. M. T.). This represents about one-half and one-tenth, respectively, the concentration in the liver and ten times and eight times the concentration in the blood. Lomholt did not analyze the bile. Ludwig and Zillner found 1.5 mg. of mercury per hundred cubic centimeters in the bile of one patient, about one-fifth the concentration in the liver, and they found none in another patient with a lower concentration in the liver. The values and ratios in the two series are comparable. Both show a rather wide variation. In both, the patients with the higher concentration in the bile had the higher concentration in the liver, and two of our patients also had a higher concentration in the blood, the latter relation being the closer. However, the number is too small to establish these correlations, especially since it is not known how long the bile was retained in the gallbladder. In any case, how-

TABLE 7.—*Amount of Mercury (Mg.) Stored in the Liver and in the Kidneys*

Patients	J.T.N.	L.R.O.	W.M.T.	Average
Dose of mercury bichloride, Gm.	2.5	5.5	1	3
Days before death	6	9	8	8
Weight of liver, Gm.	1,950	1,700	2,220	.....
Mercury, mg. per hundred grams	2.5	2.58	1.04	.....
Mercury, mg. in liver	48.8	43.9	23.4	38.7
Weight of kidneys, Gm.	480	460	420	.....
Mercury, mg. per hundred grams	3.5	3.32	2.38	.....
Mercury, mg. in kidneys	16.8	15.2	10.1	14.0
Mercury, mg. in the liver and kidneys	65.6	59.1	33.5	52.3

ever, the concentration of mercury in the bile is materially lower than that in the liver and materially higher than that in the blood.

Calculating the total daily biliary excretion by multiplying the concentration of mercury by the normal output of bile (from 500 to 1,100 cc.) leads, in the one case (L. R. O.) in which the figures are available, to higher quantities of mercury for the biliary excretion (from 6.1 to 13.4 mg.) than for the excretion in the feces, which averaged 1.35 mg. per day for the last five days of life. The contradiction might be explained by extensive reabsorption of mercury in the bile, but this is rather improbable in view of the fact that enteritis, diarrhea or scanty volume of bile may be present, as the patient is in a state of considerable shock, or that the bile from the gallbladder may become concentrated and therefore not represent normal bile. Consequently all that can be affirmed is that some mercury present in the feces comes from the bile.

Liver and Kidneys.—The total mercury content of the liver and kidneys is shown for our patients in table 7. It is about three times as high in the liver as in both kidneys (the concentration being about one and a half to two times as high in the kidneys).

Entire Body.—The total mercury content of the body after poisoning from mercury bichloride may be estimated with fair approximation from the data of table 1 by assuming an average mercury content of 0.30 mg. per hundred grams, exclusive of the liver and kidneys, which gives an estimate of 180 mg. of mercury for a person weighing 60 Kg. Adding the amount of mercury found in the liver and kidneys, about 60 mg., the total mercury content is approximately 240 mg. This amount closely approximates the acutely fatal parenteral dose for animals, from 4 to 10 mg. per kilogram (equivalent to from 240 to 600 mg. for a man weighing 60 Kg.). As it is deposited in the organs the mercury is probably inactivated, but this quantity must have passed through the blood in active form fairly acutely, so that the coincidence is probably significant. However, if the same amount had accumulated gradually, as it does in mercurial therapy, its significance would be quite different.

CONCLUSIONS

The distribution of mercury was studied at autopsy in the organs of three patients who died of typical poisoning from mercury bichloride. The results confirm those given in the few reliable reports of cases in the literature. There is a surprising quantitative uniformity in the data for different patients, although the dosage has some effect. The concentration of mercury is uniformly highest in the kidneys (average, 3.8 mg. per hundred grams of moist organ, using the medians of the reliable analyses given in the literature); the liver follows, with about one half to two thirds of the concentration in the kidneys; then the spleen, with one seventh; the intestines, with one ninth; the heart, skeletal muscle and lungs, with about one fifteenth (0.2 to 0.3 mg. per hundred grams), and finally the brain, with one twenty seventh. The concentration of mercury in the blood was between 0.015 and 0.12 mg. per hundred cubic centimeters, about one fortieth of that in the kidneys. The concentration in the ascitic fluid was even lower; that in the bile was variable but always higher than that in the blood and lower than that in the liver. The total mercury content of the liver was about three times that of both kidneys.

CHOLESTEROL CONTENT OF WHOLE BLOOD IN PATIENTS WITH ARTERIAL HYPERTENSION

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The demonstration by Anitschkow [1] in 1912 that the feeding of pure cholesterol to rabbits produced lesions of the large arteries closely simulating human arteriosclerosis suggested the view, championed by the Aschoff school, that atheroma in man is primarily due to impregnation of the intima with lipoid material. With the development of satisfactory methods for the measurement of the lipoid content of the blood, many investigators have studied the cholesterol partition in the blood of persons with hypertension and arteriosclerosis, with the thought that the presence of a high cholesterol content might, in conformity with the experimental results, be of pathogenic significance in these conditions.[2] The demonstration of a consistent variance from the norm of the cholesterol metabolism in patients with hypertension, who are at least potentially subject to arteriosclerosis, might, besides helping to explain the close association which exists between these two conditions, disclose a new avenue for therapeutic approach.

The studies dealing with the cholesterol partition in the blood of patients with arterial hypertension have given conflicting results. As will be seen, many of them are open to serious criticism. In 1917 Denis,[3] using the method of Bloor, found that the cholesterol content was not increased above normal in eighteen patients with hypertension, twelve of whom had arteriosclerosis. She also found that renal impairment unassociated with azotemia did not appreciably influence the cholesterol level. In the same year Gorham and Myers,[4] using their own

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1. Anitschkow, N., in Cowdry, Edmund V.: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933, p. 271.

2. The recent demonstration by Dr. T. H. Paul of Boston (Am. Heart J. **10**:328 [Feb.] 1935) that the escape of cholesterol into the lumen of a coronary artery from a ruptured atheroma may result in coronary occlusion by acting as an embolus increases our interest in the cholesterol problem.

3. Denis, W.: Cholesterol in Human Blood Under Pathological Conditions, J. Biol. Chem. **29**:93, 1917.

4. Gorham, F. D., and Myers, V. C.: Remarks on the Cholesterol Content of Human Blood, Arch. Int. Med. **20**:599 (Oct.) 1917.

method and assuming the average normal cholesterol content of human blood to be 160 mg. per hundred cubic centimeters of blood, studied twenty patients with hypertension, eight of whom had arteriosclerosis. The average cholesterol value for the group was 190 mg. per hundred cubic centimeters, with high and low values of 270 and 150 mg., respectively.

In 1924 Pribram and Klein,[5] using the method of Authenreith and Funk, concluded, as the result of eighty-seven determinations, that most patients with hypertension have hypercholesteremia. No control determinations on normal persons were reported. Similar conclusions were reached by Westphal,[6] who found hypercholesteremia in 71 per cent of eighty cases, and by Richard and Roesch,[7] who made studies in a similar number of cases. These investigators used a modification of the method of Authenreith and Funk and the method of Grigaut, respectively. Apparently no control series were observed. The confusion introduced by the multiplicity of methods for the determination of the cholesterol content was emphasized by Weidman and Sunderman [8] who, in reviewing the normal values for cholesterol content in man and animals as given by approximately eleven methods in use up to that year, concluded that the various technics had been so habitually modified by succeeding workers as to give inconstant values for the normal content.

The occurrence of hypercholesteremia in patients with hypertension has likewise been reported by Weil, Guillaumin and Abricoff,[9] who in eighteen instances professed to find a relationship between the cholesterol level and the height of the blood pressure. However, they failed to give the method used, and their report contains no observations on controls. Alvarez and Neuschlosz [10] in 1931 studied the cholesterol content of the serum in patients with hypertension by a new technic. Such serum was brought in contact with a known amount of cholesterol for a period of twenty-four hours, and the change in cholesterol content was deter-

5. Pribram, H., and Klein, O.: Ueber den Cholesteringehalt des Blutserums bei arteriosklerotischem Hochdruck, Med. Klin. **20**:572 (April 27) 1924.

6. Westphal, K.: Pathogenesis of Essential Arterial Hypertension: Cholesterol a Tonus-Increasing Substance in Essential Hypertension and Its Relation to Other Pathogenic Factors, Ztschr. f. klin. Med. **101**:584, 1925.

7. Richard, G., and Roesch, J.: Amount of Cholesterol in Eighty Subjects with Hypertension, Bull. Acad. de méd., Paris **95**:363 (March 30) 1926.

8. Weidman, F. D., and Sunderman, F. W.: Hypercholesteremia: I. The Normal Blood Cholesterol Figures for Man and for the Lower Animals, Arch. Dermat. & Syph. **12**:679 (Nov.) 1925.

9. Weil, M. P.; Guillaumin, C. O., and Abricoff, L.: Contribution à l'étude des obèses: L'état de pléthore, Ann. de méd. **23**:328, 1928.

10. Alvarez, C., and Neuschlosz, S. M.: Untersuchungen über das Blutcholesterin bei arteriellem Hochdruck, Klin. Wchnschr. **10**:244 (Feb. 7) 1931.

mined by means of tests made before and after this procedure. In twenty-one of the twenty-five cases in which tests were made there was less cholesterol in the serum after the twenty-four hour period than before, while in the serum of patients not suffering from hypertension the cholesterol level was found to be increased after twenty-four hours. This Alvarez and Neuschlosz interpreted as indicating a supersaturation (*Uebersättigung*) of serum by cholesterol in patients with arterial hypertension. Medvei,[11] in repeating these observations, found that the differences in saturation in his series did not significantly exceed the experimental error of the method. Furthermore, the average cholesterol level in untreated serum of fifteen patients with hypertension was 154 ± 9.56 mg. per hundred cubic centimeters as compared with an average level of 119 ± 4.57 mg., the value obtained in a like number of observations on controls. This is the only study we have encountered in which statistical criteria were utilized, and the difference in values was not significant. Wacker and Fahrig [12] reported an increase of all lipoid complexes of the blood in cases of arterial hypertension. Using the Authenreith and Funk technic, they found an average cholesterol value of 207.4 mg. per hundred cubic centimeters in sixteen instances, as compared with an average value of 152.17 mg. for nineteen normal persons. The statistical significance of this difference cannot be calculated from their data.

Recently Bruger and Poindexter [13] studied the cholesterol content of the plasma in patients with uncomplicated obesity. Rarely was an abnormal value, by their criteria, encountered in this group. Three of thirteen patients in whom the obese state was complicated by essential hypertension had hypercholesteremia, and in one obese patient with arteriosclerosis an increased plasma cholesterol content was observed. Bruger and Poindexter regarded these results as significant.

We believe that the contention of those who believe that hypercholesteremia accompanies arterial hypertension remains to be proved. The reported studies have been for the most part inadequately controlled. The normal range of values, including the experimental error of the method used, has not been determined by each investigator for himself, and the "error of sampling," as revealed by statistical analysis, has not received sufficient attention. Furthermore, in many of the studies, con-

11. Medvei, C. V.: Zur Frage des Blutcholesterins bei arteriellem Hochdruck, Klin. Wchnschr. **11**:414 (March 5) 1932.

12. Wacker, L., and Fahrig, C.: Ueber die mineralischen und lipoiden Bestandteile des Blutserums bei der essentiellen Hypertension im Vergleich zu den physiologischen Verhältnissen, Klin. Wchnschr. **11**:762 (April 30) 1932.

13. Bruger, M., and Poindexter, C. A.: Relation of Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteo-Arthritis and Arteriosclerosis), Arch. Int. Med. **53**:423 (March) 1934.

ditions which of themselves are known to elevate the cholesterol content of the blood and which may accompany arterial hypertension have not been rigorously excluded. Among these conditions may be listed diabetes mellitus,[14] hyperthyroidism,[15] the nephrotic syndrome in glomerulonephritis [16] and obstructive disease of the biliary tract.[17]

In this study we have attempted to elucidate and obviate complicating factors and to present adequately controlled data with a statistical evaluation of their significance. It will be shown that in our series essential hypertension with or without arteriosclerosis was not accompanied by hypercholesteremia.

MATERIAL AND METHOD

Our series consisted of two groups of patients. Group 1 comprised fifty-three hospitalized patients in whom the systolic blood pressure consistently exceeded 150 mm. of mercury. There were twenty-four men and twenty-nine women ranging in age from 22 to 90 years, the average age being 61.2 years. The patients received a uniform hospital diet. Evidence of arteriosclerosis was carefully sought for by palpation of peripheral arteries and fluoroscopic examination of the aorta. The state of the arterioles was judged by ophthalmoscopic examination of the ocular fundi. The degree and extent of vascular damage were arbitrarily graded on the basis of from 0 to 3 plus. The presence of inflammatory renal disease was rigorously excluded, and the status of renal function was determined by the following tests: (1) the dilution and concentration test of Volhard; (2) the phenolsulphonphthalein test; (3) the test for urea clearance; (4) the creatinine test of Majors, and (5) the determination of the urea nitrogen content of the blood. Renal impairment was considered to be present if at least two of these tests gave abnormal results.

The basal metabolic rate was determined in forty instances. It is to be emphasized that this was done as a routine procedure. In no instance was there clinical evidence of thyroid dysfunction. The sugar content of the blood during fasting was determined in all but two of the patients. It was significantly elevated in only two instances, but the values for cholesterol were not abnormal; hence, for the purposes of this study it was not deemed necessary to determine the dextrose tolerance.

Control determinations of the cholesterol content were made on a group of forty-five hospital and dispensary patients (group 2). This group consisted of twenty-five male and twenty female patients, varying in age from 17 to 81 years, with an average age of 49.8 years. Unfortunately it was impractical to study this group as carefully as the patients with hypertension, but so far as possible patients with minor ailments not due to a disturbance of metabolism were chosen. None of

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14. Gray, H.: Lipoids in One Thousand Diabetic Bloods with Special Regard to Prognosis, Am. J. M. Sc. **168**:35 (July) 1924.

15. Hurxthal, L. M.: Blood Cholesterol and Thyroid Disease: III. Myxedema and Hypercholesteremia, Arch. Int. Med. **53**:762 (May) 1934.

16. Volhard, F., and Suter, F.: Nieren und ableitende Harnwege, Berlin, Julius Springer, 1931, p. 314.

17. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams and Wilkins Company, 1931, p. 247

the patients had hypertension, hypothyroidism, diabetes mellitus, nephritis or disease of the biliary tract.

It should be noted that all the females in both groups had passed the menopause. Careful attention was paid to this point because Okey and Boyden [18] have demonstrated the profound changes occurring in the cholesterol level of the blood during the phases of the menstrual cycle.

In every instance, blood for the determination of the cholesterol content was drawn before breakfast. The method of Bloor, Pelkan and Allen [19] was used. The experimental error in our laboratory was found to be 5 per cent. Bloor [20] stated that the average normal content by this method is about 200 mg. per hundred cubic centimeters of blood, with a range of between 100 and 230 mg.

RESULTS

In table 1, the pertinent data are given for the patients with hypertension, and in table 2, those for the control group. The patients are listed in the tables according to increasing magnitude of cholesterol values.

The fifty-three patients with hypertension had an average cholesterol content of whole blood of 167.5 ± 3.0 mg. per hundred cubic centimeters. The values for the control group averaged 177.3 ± 4.6 mg. per hundred cubic centimeters. The difference in values, as indicating a trend, is not statistically significant. No patient in group 1 had a cholesterol level exceeding 230 mg. per hundred cubic centimeters of blood, the upper limit of normal values according to Bloor. In the control group (group 2) one value of 230 mg. and one of 282 mg. per hundred cubic centimeters were encountered. Both of the patients suffered from malnutrition, a finding which is consistent with the conception that cachexia may cause hypercholesteremia.[21]

The spread of values for the two groups may be expressed graphically as curves of distribution (chart). The curve for the control group is "skewed," which probably indicates that more uncontrolled factors were at work in this group and that they tended to influence the cholesterol level primarily in one direction, i. e., to increase it. We may call attention to one of these factors, namely, divergence from average body weight.

Table 1 shows that of thirteen patients with hypertension with a cholesterol level exceeding 180 mg. per hundred cubic centimeters of

18. Okey, K., and Boyden, R. E.: Studies of the Metabolism of Women: III. Variations in the Lipid Content of Blood in Relation to the Menstrual Cycle, J. Biol. Chem. **72**:261, 1927.

19. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, J. Biol. Chem. **52**:191, 1922.

20. Bloor, W. R.: Personal communication to the authors.

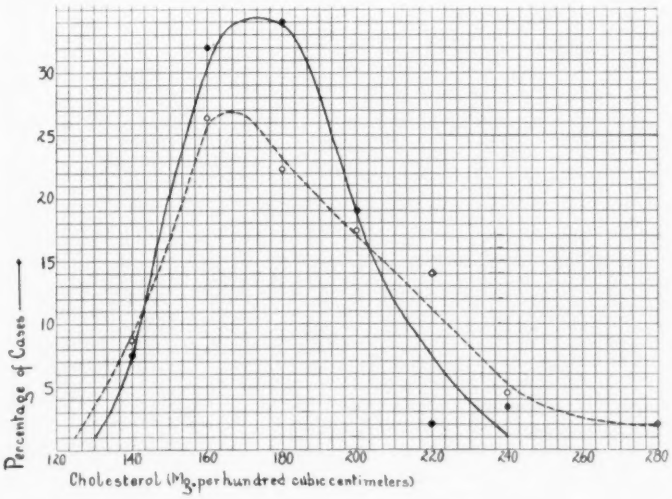
21. Peters and Van Slyke,[17] p. 245.

TABLE 1.—*Values for Cholesterol and Pertinent Data on Fifty-Three Patients with Arterial Hypertension (Group 1)*

Patient	Age	Sex	Average Blood Pressure	Known Duration of Hypertension	Cholesterol, Mg.*	Arteriosclerosis	Renal Impairment	Percentage Overweight or Underweight	Basal Metabolic Rate	Sugar, Mg.*	Urea Nitrogen, Mg.*	Calcium, Mg. per 100 Cc. of Serum
1	54	M	210/120	3 yr.	125	+	+	+16	+ 0.9	124	14.8	10.3
2	40	M	160/ 80	?	129	+	..	0	—20.0	94	....	....
3	54	M	200/110	1 yr.	137	++	..	+ 8	?	110	13.0	11.1
4	63	M	165/105	?	139	++	..	+30	—19.0	120	11.1	11.2
5	46	F	200/100	4 yr.	144	0	..	—12	— 2.0	92	15.0	9.6
6	80	M	210/130	10 yr.	145	++	+	— 9	+20.0	104	38.4	9.6
7	75	F	215/115	?	145	+++	..	—20	?	120	16.0	?
8	72	F	180/100	?	145	++	..	+21	?	120	16.9	11.0
9	70	F	220/110	?	145	+	..	+18	+ 0.5	104	12.0	?
10	72	M	170/ 90	1 yr.	145	++	..	+ 5	— 4.0	132	29.0	?
11	41	F	220/130	3 yr.	145	+	..	+ 8	?	110	17.9	?
12	67	F	175/110	?	151	0	..	+33	—23.0	220	11.6	9.2
13	22	M	170/110	1 yr.	152	0	..	+ 8	+ 2.0	112	17.1	?
14	67	M	150/100	8 yr.	153	+	..	+ 4	—21.0	96	20.5	?
15	57	M	210/110	12 yr.	154	+	..	— 5	— 8.3	110	14.3	9.0
16	63	F	170/110	10 yr.	155	0	..	0	—23.0	94	11.0	11.4
17	51	M	220/160	10 yr.	155	++	..	0	+ 5.0	124	12.7	10.2
18	62	M	170/110	?	155	+++	..	+ 5	— 2.2	110	23.0	?
19	52	F	160/ 85	?	155	0	..	+ 8	—30.0	92	13.0	?
20	63	M	220/110	5 yr.	155	++	..	— 5	?	105	23.6	?
21	70	F	200/ 80	?	159	+	..	+20	— 7.7	104	15.4	12.5
22	49	F	255/150	8 yr.	159	+	..	+38	— 0.9	128	13.3	11.1
23	57	M	200/100	6 yr.	162	+	..	—	— 6.0	106	15.0	11.6
24	80	F	170/ 80	?	163	0	..	+ 4	?	138	10.7	10.1
25	73	M	220/130	4 yr.	164	+++	+	— 4	— 4.0	108	15.3	9.7
26	79	F	230/ 90	10 yr.	166	+	..	—16	?	110	16.9	?
27	60	F	180/ 80	?	166	++	..	—31	+15.6	126	13.4	?
28	62	M	205/105	4 yr.	167	+	+	0	?	?	18.8	?
29	65	F	245/ 85	?	167	+	..	— 2	—12.0	120	15.0	?
30	68	F	210/115	15 yr.	170	+	..	0	—13.0	104	18.8	?
31	69	M	165/ 95	?	170	0	..	+13	?	100	17.3	?
32	37	M	160/120	½ yr.	171	++	..	— 5	—19.0	114	13.6	10.2
33	64	F	180/110	?	175	++	..	— 3	—10.0	104	21.4	?
34	59	F	180/110	10 yr.	175	+	..	+17	—15.0	104	22.4	?
35	58	F	150/100	?	175	0	..	+64	—13.0	118	18.7	10.2
36	45	F	180/110	1 yr.	175	0	..	+20	+ 1.0	120	15.3	?
37	65	F	155/ 85	?	180	0	..	0	—10.0	104	13.3	10.6
38	61	F	230/150	?	180	0	..	+43	—10.0	121	19.0	?
39	34	M	235/135	12	180	+	+	— 3	—24.0	110	31.0	?
40	90	M	215/ 90	?	180	+++	..	—15	?	108	20.7	?
41	60	F	175/100	?	182	+	..	— 3	— 2.0	110	13.1	10.4
42	56	M	170/110	8 yr.	185	++	..	— 8	—10.8	104	15.0	10.0
43	66	F	170/ 90	6 yr.	185	+	..	— 7	— 0.8	114	15.4	10.0
44	59	F	160/ 90	5 yr.	185	0	..	— 2	+ 3.6	120	15.0	?
45	77	M	215/ 95	?	188	+	..	— 5	?	212	20.0	?
46	55	M	200/100	17 yr.	191	+	..	—11	+10.0	102	17.6	10.2
47	74	F	155/ 90	?	195	+	..	+ 6	?	114	13.0	?
48	60	F	200/ 90	?	196	++	..	—18	+11.8	114	13.6	10.7
49	78	F	220/ 70	18 yr.	196	++	+	0	?	136	13.6	9.8
50	58	M	220/110	7 yr.	198	++	..	—13	+ 3.0	116	25.6	?
51	62	F	160/100	12 yr.	203	+	..	—23	—12.0	104	15.6	9.7
52	50	F	180/110	?	222	0	..	— 6	— 5.0	?	16.6	?
53	73	M	155/ 90	?	222	++	..	—13	+ 5.0	106	13.3	?

* The values for cholesterol, sugar and urea nitrogen are given in milligrams per hundred cubic centimeters of blood. The average value for cholesterol was 167.5 ± 3.0; that for calcium, 10.3 ± 0.17.

blood only one was slightly overweight, while the remainder were of normal weight or underweight. The average divergence from normal weight in this group was minus 7.7 ± 1.9 pounds (3.49 ± 0.86 Kg.), while in the remaining thirty-nine patients, it was plus 6.8 ± 2.8 pounds (3.08 ± 1.27 Kg.). This difference could occur by chance only once in several thousand times and hence cannot be without significance. However, all underweight persons in this group did not tend to have higher cholesterol levels (cases 5, 7, 26, 27 and others). We may interpret this as indicating that in a fair proportion of underweight persons some factor or factors, at present obscure, are at work which tend to elevate the cholesterol content of the blood.



Curves of distribution of cholesterol values for patients with and without hypertension. The solid dots indicate values for the patients with hypertension (group 1), and the open circles, those for the control group (group 2).

The same phenomenon was observed in the control group. It accounts in part at least for the "skew" in the curve of distribution previously mentioned, as an attempt was made to include in this group a large proportion of underweight persons. The average divergence from normal weight in nineteen patients in whom the cholesterol content of the blood exceeded 180 mg. per hundred cubic centimeters was minus 9.4 ± 3.5 pounds (4.26 ± 1.59 Kg.), while the remaining twenty-six patients were heavier than the average normal weight by an average of 1.3 ± 3.4 pounds (0.59 ± 1.54 Kg.).

It is of interest that Gray [14] noted a similar phenomenon in diabetic patients. He found that the amount of blood fat, including cholesterol,

TABLE 2.—*Values for Cholesterol and Pertinent Data on the Control Group*

Name	Age	Sex	Cholesterol, Mg. per 100 Cc. of Whole Blood	Percentage Overweight or Underweight	Diagnosis
J. B.	73	M	123	0	Coronary sclerosis
J. E.	21	M	133	−21	Asthma
B. T.	24	M	134	0	Normal
E. N.	49	F	138	− 2	Normal
M. B.	38	M	142	+ 4	Fractured leg
J. Y.	17	M	144	− 6	Normal
A. D.	39	M	146	+49	Peptic ulcer
B. B.	53	F	147	+11	Normal
R. A.	40	M	151	+16	Normal
C. K.	61	M	153	+ 4	Normal
L. M.	18	M	153	+ 9	Dementia praecox
J. P.	52	M	153	−11	Amnesia
A. R.	71	M	154	−12	Hypertrophy of the prostate gland
M. H.	50	F	156	− 1	Normal
M. D.	62	F	156	+39	Cardiac failure
M. K.	49	M	160	+31	Normal
E. G.	44	F	164	−21	Normal
W. C.	50	M	168	−14	Normal
H. K.	56	F	168	− 7	Mitral stenosis
E. H.	52	F	173	+16	Normal
M. B.	32	F	173	− 2	Normal
I. S.	54	F	176	−18	Normal
F. T.	58	M	176	− 6	Normal
J. B.	24	M	180	− 1	Epilepsy
E. P.	42	M	180	−22	Pellagra (?)
B. A.	52	F	180	−11	Normal
H. L.	56	F	181	−40	Paranoia
G. O.	36	M	184	−21	Healed tuberculosis
C. H.	31	M	185	+10	Chronic bronchitis
E. F.	41	F	185	0	Neurasthenia
G. E.	81	M	188	+ 6	Herpes zoster
M. D.	34	M	190	−15	Peptic ulcer
E. S.	45	M	191	+16	Chronic iritis
H. L.	46	F	200	−27	Normal
C. M.	46	M	201	+ 4	Migraine
M. O.	76	F	202	0	Senile dementia
A. D.	72	F	202	−11	Senile dementia
A. W.	57	M	203	−24	Cardiospasm
H. E.	47	F	204	+ 4	Gastro-enteritis
A. E.	40	F	206	− 6	Angina pectoris
M. F.	75	F	218	− 4	Senile dementia
W. R.	44	M	220	+ 3	Arthritis of the wrist
I. T.	60	F	226	−20	Fracture of the leg
F. L.	75	M	230	−35	Emaciation
J. V.	72	F	282	−20	Emaciation

The average value for cholesterol was 177.3 ± 4.6.

was 40 per cent higher in diabetic patients who were over 10 per cent underweight. He attributed this to more severe diabetes in these patients, but our data suggest that some factor other than diabetes alone must be taken into account.

In the last column of table 1 are listed the serum calcium values for twenty-five patients with arterial hypertension as determined by the Clark-Collip modification [22] of the Kramer-Tisdall method. These values bear no relation to the cholesterol level and all lie within the normal range of from 9 to 11 mg. per hundred cubic centimeters. They are included in the table as a matter of interest, because some observers [12] have found a slightly lowered serum calcium level in patients with arterial hypertension.

Influence of Arteriosclerosis on the Cholesterol Content of the Blood.—Thirteen of the 53 patients with hypertension had little or no evidence of vascular damage. The blood cholesterol level for the group averaged 169.7 ± 5.6 mg. per hundred cubic centimeters, with minimum and maximum values of 144 and 222 mg., respectively. For eighteen patients having from moderate to pronounced arterial disease the cholesterol content averaged 164.0 ± 4.8 mg. per hundred cubic centimeters, the lowest single value being 137 mg. and the highest, 198 mg. In this group of patients, then, there was no correlation between the cholesterol content of the blood and the presence or absence of vascular disease.

Correlation with Lowered Basal Metabolic Rate.—As previously noted, determination of the basal metabolic rate was conducted on forty of the patients with hypertension. In a surprisingly large number (42.5 per cent) the basal metabolic rate was lower than minus 10, reaching minus 20 or lower in six instances. None of these patients had the clinical symptoms of hypothyroidism or of any other endocrine dyscrasia. The average cholesterol content for the group with rates of minus 10 or lower was 167.2 ± 4.3 mg. per hundred cubic centimeters of blood, which is not significantly different from the average value of 166.5 ± 4.8 mg. for the remaining twenty-two patients with metabolic rates above minus 10.

These findings are of interest. We believe that the large number of low values for this group of patients is due in part at least to the fact that they were hospitalized during the determinations and that repeated readings were made until it was reasonably certain that a true basal metabolic rate was being measured. Hurxthal [23] recently emphasized the fact that a lowered basal metabolic rate is encountered in many conditions but that if true hypothyroidism is present it is quite uniformly accompanied by hypercholesteremia. This finding is so constant that it may be used in differential diagnosis. Our results are in conformity

22. Hawk, P. B., and Bergheim, O.: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1931, p. 460.

23. Hurxthal, L. M.: Blood Cholesterol and Hypometabolism: Suprarenal and Pituitary Deficiency, Obesity and Miscellaneous Conditions, Arch. Int. Med. **53**:825 (June) 1934.

with this conception, at least so far as they clearly show that a lowered basal metabolic rate may be encountered in the absence of clinical hypothyroidism and that under these circumstances the blood cholesterol level is not elevated.

CONCLUSIONS

The data presented in this study indicate that:

Uncomplicated arterial hypertension is not accompanied by hypercholesteremia.

Vascular degeneration and/or renal impairment occurring with arterial hypertension do not elevate the cholesterol level of the blood.

Higher values for cholesterol are found more frequently among underweight than among obese persons.

A low basal metabolic rate in persons with arterial hypertension, if unaccompanied by clinical symptoms of hypothyroidism, does not produce hypercholesteremia.

Miss M. Louisa Long and Miss Elsie Hill gave technical assistance, and Dr. A. L. Koehler furnished data on some of his patients.

CHLOROPHYLL AND REGENERATION OF THE BLOOD

EFFECT OF ADMINISTRATION OF CHLOROPHYLL DERIVATIVES TO PATIENTS WITH CHRONIC HYPOCHROMIC ANEMIA

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Chronic hypochromic anemia is characterized primarily by a deficiency of hemoglobin. Iron is adequately effective in treatment, although this element composes only a small portion of the hemoglobin molecule. It is thus of interest to inquire whether other factors may be lacking besides iron and, if so, whether these factors when supplied can assist in the formation of hemoglobin.

In addition to a lack of iron there may occur sometimes a deficiency of other substances useful in the formation of hemoglobin, such as substances which occur in liver. Material contained in bile pigment perhaps may be wanting. Bile pigment [1] has been shown to exert a favorable effect on the regeneration of hemoglobin in cases of chronic hypochromic anemia. As a working hypothesis it has been assumed that the pigment aids in the synthesis of hemoglobin by supplying material suitable for the heme portion of the molecule. Because of the similarity of chlorophyll to this pigment, the present study has been made to determine the effect of chlorophyll and its derivatives on the regeneration of hemoglobin in cases of chronic hypochromic anemia.

RELATIONSHIP OF CHLOROPHYLL AND HEMOGLOBIN

Biologic Relationship.—For many years both the lay and the medical public have believed green vegetables to possess an indefinite but probable value in building blood. Abderhalden [2] in his textbook suggested that blood pigment might be made from plants. The fact that herbivora build hemoglobin on a diet composed of leafy greens invites the hypothesis that derivatives of chlorophyll may be used in making hemo-

The expenses of this investigation were borne in part by a grant from the J. K. Lilly gift to the Harvard Medical School.

From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Patek, A. J., Jr., and Minot, G. R.: Am. J. M. Sc. **188**:206, 1934.

2. Abderhalden, E.: Lehrbuch der physiologischen Chemie in dreissig Vorlesungen, ed. 3, Berlin, Urban & Schwarzenberg, 1914.

globin. Certainly the ultimate products, that is to say amino-acids, must be used for this. Whether it is possible for the body to use building stones preformed from the food, such as the pyrrols or porphyrins, in the synthesis of hemoglobin has been neither proved nor disproved.

Much phyllo-erythrin, for example, appears in feces of cattle. Part, however, of this pigment derived from chlorophyll is recovered in bile,[3] which indicates some absorption. But, as Marchlewski [4] commented, there is no reason for assuming that chlorophyll can be used for the formation of hemoglobin. The absorption does not imply necessarily a useful purpose. Fischer and Hendschel,[5] indeed, expressed the opinion that it plays no part in nutrition. The cow has been shown to decompose chlorophyll in its third and fourth stomach to the porphyrin stage.[6] Its long intestine is well suited to the thorough digestion of the cellulose material that envelops the pigment. The cow, therefore, is able to utilize greenstuffs better than man. This may account for the failure to demonstrate in man a significant hemoglobin-enriching effect from feeding spinach and other greenstuffs. If benefit is derived from chlorophyll pigment in these foods it is probably by a slow process.

Chemical Relationship.—Added to the biologic is a chemical relationship between chlorophyll and hemoglobin. This was suggested by Verdeil [7] in 1851 and substantiated in 1879 by Hoppe-Seyler,[8] who showed a similarity between hematin and chlorophyll derivatives. Later Nencki, Zaleski, Schunck and Marchlewski [9] obtained hemopyrrols from both sources. Until the time of Willstätter's work [10] (1906-1913), the exact nature of chlorophyll and its mineral component was not established. Willstätter recognized it as an unstable water-insoluble magnesium compound characterized by ester groups of methyl and phytyl alcohol. A knowledge of the molecular structure was gained through the research of Hans Fischer [11] and later elaboration by Conant.[12] The subject was reviewed recently by Schertz,[13] Armstrong [14] and Fischer.[15]

3. Broun, G. O.; McMaster, P. D., and Rous, P.: J. Exper. Med. **37**:699, 1923.

4. Marchlewski, L., and Urbańczyk, W.: Biochem. Ztschr. **263**:166, 1933.

5. Fischer, H., and Hendschel, A.: Ztschr. f. physiol. Chem. **198**:33, 1931; **206**:255, 1932; **216**:57, 1933.

6. Rothemund, P., and Inman, O. L.: J. Am. Chem. Soc. **54**:4702, 1932.

7. Verdeil, M. F.: Compt. rend. Acad. d. sc. **33**:689, 1851.

8. Hoppe-Seyler, F.: Ztschr. f. physiol. Chem. **3**:339, 1879; **4**:193, 1880.

9. Marchlewski, L.: Die Chemie der Chlorophylle und ihre Beziehung zur Chemie des Blutfarbstoffs, Braunschweig, F. Vieweg & Son, 1909.

10. Willstätter, R., and Stoll, A.: Untersuchungen ueber Chlorophyll, Berlin, Julius Springer, 1913.

11. Fischer, H.: Ber. d. deutsch. chem. Gesellsch. **60**:2611, 1927.

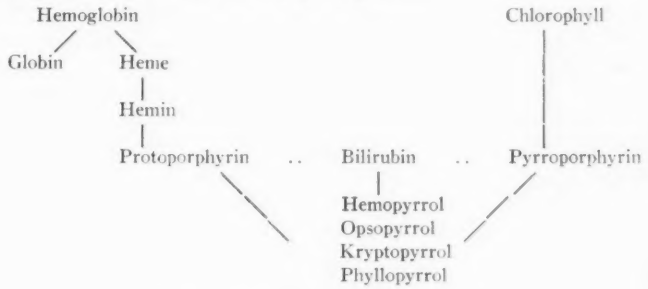
12. Conant, J. B., and Dietz, E. M.: J. Am. Chem. Soc. **55**:839, 1933.

13. Schertz, F. M.: Quart. Rev. Biol. **3**:459, 1928.

14. Armstrong, K. F.: Chem. & Indust. **52**:809, 1933.

15. Fischer, H.: J. Chem. Soc. London **1**:245, 1934.

The following diagram gives a scheme of the chemical relationship of hemoglobin, bilirubin and chlorophyll pigments:



EXPERIMENTATION ON ANIMALS

The first person to attempt to demonstrate in animals a hematopoietic effect of chlorophyll was Emil Bürgi,[16] who in 1916 observed that rabbits rendered anemic by bleeding recovered more rapidly when chlorophyll was added to their diet. J. M. D. Scott[17] in 1923 noted that rats fed white bread, milk and leafy greens failed to have anemia after repeated small measured losses of blood, in contrast to rats that had been fed a diet of white bread and milk alone. E. Scott and Delor[18] in 1933 reported experiments in which the anemia of rats induced by a diet of milk was relieved by the administration of an iron-free and copper-free extract of alfalfa. Saunders[19] in 1926, Zih[20] in 1933 and others[21] reported on the regenerative effect on hemoglobin of feeding chlorophyll to animals with experimental anemia. On the contrary, Guerrini[22] recently described a hemolytic effect resulting from photosensitivity after the intravenous injection of chlorophyll in albino rats.

The diverse results and interpretations of earlier writers are confusing. Most of the work was done before pure preparations of chlorophyll were available, and little effort has been made to exclude the possibility of side effects from mineral contaminants.

THE DISEASE IN MAN

A good diet has been considered requisite for the cure of nutritional hypochromic anemia. Yet the addition of iron alone to a minimal or

16. Bürgi, E.: Cor.-Bl. f. schweiz. Aerzte **46**:449, 1916.
17. Scott, J. M. D.: Biochem. J. **17**:157, 1923.
18. Scott, E., and Delor, C. J.: Ohio State M. J. **29**:165, 1933.
19. Saunders, C. W.: Proc. Soc. Exper. Biol. & Med. **23**:788, 1926.
20. Zih, A.: Arch. f. d. ges. Physiol. **231**:510, 1933.
21. Aoki, S.: Sei-I-Kwai M. J. **50**:1, 1931; abstr., Chem. Abstr. **26**:3847, 1932. Sagastume, C., and Pezzani, J.: Rev. Facult. d. cienc. quim., Univ. la Plata **7** (pt. 2) 7, 1930; abstr., Chem. Abstr. **25**:3080, 1931.
22. Guerrini, G.: Boll. d. Soc. ital. di biol. sper. **7**:835, 1932.

even to an inadequate diet corrects the anemia rapidly. How does iron do this when globin and heme pigments are involved in the synthesis of hemoglobin? If a patient with anemia is given a diet rich in meat, greens and fruit one does not see a sharp response in the hemoglobin content or the red blood cell count. The hemoglobin content, however, that one estimates from a sample of the peripheral blood does not necessarily reflect the underlying state of the tissue, such as the blood reserve. There is obviously a blood potential in the total organism which a determination on a sample of blood may not indicate. A "good" diet, then, might be useful in a way which the present standards of measure do not show, at least in a short space of time.

The problem is not so much whether factors other than iron do play a rôle as whether they can play a rôle in the formation of hemoglobin. If it can be shown that certain substances beside iron influence the regeneration of hemoglobin in hypochromic anemia in man, as Whipple demonstrated that they do in dogs, and that these substances exert their influence in some manner other than furthering the absorption of iron, it is permissible to suppose that such substances may take part in the regeneration of hemoglobin. Otherwise it is implied that the body makes no use of these preformed substances but rather synthesizes them.

Except for reports by Bürgi [23] and his co-workers,[24] little has been recorded in the literature concerning the clinical trial of chlorophyll in the treatment of anemia. Bürgi and his associates recommended it not only in cases of anemia but also in cases of tuberculosis, cardiac disease, arteriosclerosis and mental depression because of its "tonic" benefit. Bürgi's preparation chlorosan and other proprietary remedies purporting to contain chlorophyll have been found on analysis to contain a trivial amount of the substance. For these reasons one regards Bürgi's clinical reports with skepticism.

PROGRAM AND METHODS

The present study concerned fifteen adult patients with chronic hypochromic anemia who were given chlorophyll and allied substances. Chronic hypochromic anemia serves well in the study of the regeneration of hemoglobin because the hemoglobin content is reduced much more than the red blood cells. It is a chronic disease and little subject to spontaneous fluctuation in the state of the blood. Consequently, any changes occurring during therapy in such patients would seem to be part of a causative sequel. The patients were given a house diet free from meat and eggs. Whereas it was adequate in other respects, the diet was shown in previous studies not to cause improvement of the condition of the blood in such cases. The red blood cell count, the concentration of hemoglobin and the percentage of reticulocytes were determined frequently for a control period of a week before therapy was begun. The initial red cell counts varied from 2,200,000 to 4,600,000 per cubic millimeter, and the hemoglobin content varied from 22 to

23. Bürgi, E.: Das Chlorophyll als Pharmakon, Leipzig, Georg Thieme, 1932.
24. Zickgraf, G.: München. med. Wchnschr. **79**:998, 1932.

58 per cent (Sahli). These determinations were made on alternate days on venous blood. Reticulocytes were counted daily on from 1,000 to 2,000 red blood cells.

Since the reaction of the reticulocytes is a sensitive index of the potency of the material administered to patients with anemia, the course taken by these young red cells was followed closely. This measure allows one to learn promptly the response to therapy, whereas the concentrations of the hemoglobin and the red cell count may lag considerably. In this way one may test the potency of different substances in succession on the same patient, which is a more valid procedure than to compare the response in one patient to that in another. By using the same patient for testing different materials, one period of observation serves as a control for the ensuing period.

Heretofore it has been shown that if a suboptimal dose of iron is followed by a larger dose a second reticulocyte response will occur. The validity of this comparative test was discussed by Heath [25] and Minot.[26] With this in mind, preparations of chlorophyll were given with iron after a period of medication with the latter alone, in order to see what further response, if any, they might effect.

PREPARATIONS USED [27]

There are two difficulties concerning the clinical use of preparations of chlorophyll. The first is to obtain a pure preparation, because leafy greens contain minerals, salts, vitamins and other substances in addition to chlorophyll. The chlorophyll content varies markedly with the season, the type and the condition of the plants. It would be impossible, therefore, to conclude from the feeding of greenstuffs what rôle is played by chlorophyll. The second difficulty is that pure chlorophyll is unstable and insoluble in most solvents. With it one can create only a finely dispersed state. Whatever is absorbed by feeding must be a small portion of the material administered. Just as insoluble preparations of iron are relatively ineffectual in the treatment of hypochromic anemia because of difficulty in absorption, the feeding of an insoluble material like pure chlorophyll could not be expected to produce significant changes in the blood. Reports of negative effects from the use of pure chlorophyll or pheophytin would not be surprising. Sodium chlorophyllin, a soluble salt, was therefore used by preference in this study. A further degradation product, chlorin *e*, which is likewise soluble, was tried parenterally.

The crude chlorophyll used was a tarlike paste extracted from alfalfa leaves. Natural contaminants were present, such as xanthophyll, fucoxanthin and carotinoid pigments. In five instances the material was fed in capsules. In a sixth instance it was given in 50 cc. of water to which 3 cc. of a 10 per cent solution of sodium hydroxide had been added for each 10 Gm. of paste. This made a homogeneous mixture, but it was unpalatable.

Pheophytin is pure chlorophyll from which the magnesium radical has been split off. Since pure chlorophyll loses this magnesium radical in the stomach by interaction with hydrochloric acid, pheophytin virtually had the same significance

25. Heath, C. W.: Oral Administration of Iron in Hypochromic Anemia, Arch. Int. Med. **51**:459 (March) 1933.

26. Minot, G. R.: Tr. A. Am. Physicians **49**:287, 1934.

27. The American Chlorophyll Company supplied pheophytin and sodium chlorophyllin. The crude chlorophyllin was supplied by Smith, Kline and French. Dr. Emma Dietz, of the Converse Laboratory, Harvard College, prepared the chlorin *e*.

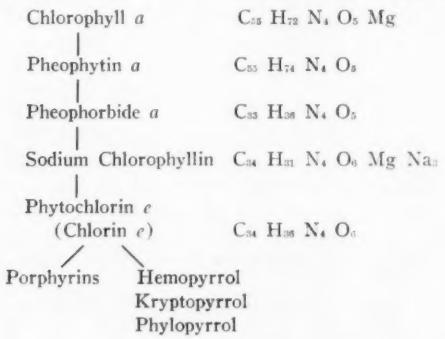
in these studies as pure chlorophyll. In three instances it was fed in capsules. In a fourth it was given in oil, but this was unpalatable.

Sodium chlorophyllin is a water-soluble salt containing the magnesium radical. It was given in solution and was not found distasteful.

Chlorin *e* is a water-soluble degradation product which lacks the magnesium radical. This was neutralized by the addition of a few drops of concentrated sodium hydroxide until p_H 7.4 was reached. It was then passed through a Berkefeld filter and stoppered in air-tight sterile bottles. Each cubic centimeter contained 0.02 Gm. of the solid material. Intragluteal injection caused moderate local pain and discoloration of the buttocks. The addition of procaine hydrochloride to the solution of chlorin *e* afforded relief.

An analysis of the iron content of these preparations was as follows: in crude chlorophyll, 23 mg. of iron per hundred grams; in pheophytin, 200 mg. of iron per hundred grams; in sodium chlorophyllin, 40 mg. of iron per hundred grams and in chlorin *e*, 165 mg. of iron per hundred grams. Therefore the amount of iron contained in the largest daily dose of these products was: for crude chlorophyll (4 Gm.), 0.9 mg. of iron; for pheophytin (1.5 Gm.), 3 mg. of iron; for sodium chlorophyllin (1.5 Gm.), 0.6 mg. of iron, and for chlorin *e* (0.1 Gm.), 0.016 mg. of iron. These amounts were relatively insignificant, since the smallest dose of ferric ammonium citrate prescribed (0.6 Gm.) contained 102 mg. of iron.

The composition of the five substances listed showed the following relationships:



OBSERVATIONS

A. Chlorophyll Products Alone.—In two separate series of observations on the same patient pheophytin was fed in amounts averaging 1 Gm. daily for seven days, without effect on the red blood cell count, the concentration of hemoglobin or the reticulocyte count. Negative results were noted also in two patients fed sodium chlorophyllin daily in amounts averaging 1.5 Gm. daily for seven days. In one case 5 cc. of chlorin *e* was injected intramuscularly daily for five days without effect.

B. Disproportionate Amounts of Chlorophyll and Iron (Administered Orally).—In three series of observations on two patients a trial period of treatment with ferric ammonium citrate in daily doses of 0.6, 0.6 and 1.8 Gm., respectively, was given for ten days. In the first case a moderate response of reticulocytes occurred; in the two others only a slight response took place. With this medication continued crude chlorophyll was added in amounts of 3, 4 and 4 Gm., respectively, for ten days, but an additional effect was not observed. Thus very small doses of iron with relatively large doses of chlorophyll were no more effective than iron alone.

TABLE 1.—*Results in Six Cases of Chronic Hypochromic Anemia of Administering Iron and Chlorophyll Products After a Period of Therapy with Iron Alone*

Days of Treatment	0.6 Gm. Daily* Case 1			4 Gm. Daily† Case 2			1.5 Gm. Daily Case 3			0.6 Gm. Daily Case 4			1 Gm. Daily Case 5			1 Gm. Daily Case 6‡		
	Red Blood Cells, Million	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Million	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Million	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Million	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Million	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Million	Hemoglobin, per Cent	Reticulocytes, per Cent
Period 1. Oral Administration of Iron and Ammonium Citrate																		
0	4.63	50	1.2	5.0	59	1.4	2.30	37	1.0	2.68	25	1.1	3.36	42	0.9	2.70	29	2.2
2	....	51	1.7	....	60	2.0	....	39	2.3	....	..	2.1	....	44	0.5	....	28	1.6
4	....	51	1.2	....	61	2.8	....	40	4.7	....	23	1.0	....	43	0.8	....	32	2.9
6	....	51	1.6	....	61	6.8	....	42	10.1	....	..	2.0	....	..	2.0	....	35	3.5
8	....	52	1.6	....	62	10.3	....	42	11.5	....	..	1.6	....	42	1.0	....	35	3.5
10	4.75	53	1.3	5.38	65	2.2	....	43	8.0	2.70	24	1.8	3.55	44	0.9	....	39	4.7
12	....	..	...	....	..	...	....	45	4.8	....	..	...	....	..	...	....	..	2.5
14	....	..	...	....	..	...	3.67	47	2.8	....	..	...	....	..	...	3.31	40	1.7
Period 2. Oral Administration of Chlorophyll Products in Addition to the Same Amounts of Iron and Ammonium Citrate as in Period 1																		
	Sodium Chlorophyllin, 0.6 Gm. Daily 5 Days			Crude Chlorophyll, 3.5 Gm. Daily 10 Days			Crude Chlorophyll, 2 Gm. Daily 5 Days			Sodium Chlorophyllin, 0.3 Gm. Daily 6 Days			Pheophytin, 1 Gm. Daily 10 Days			Pheophytin, 1 Gm. Daily 9 Days		
2	5.01	57	1.9	5.16	71	2.3	3.67	48	1.0	2.70	24	1.9	3.55	45	3.4	3.50	45	2.1
4	....	59	3.3	....	73	6.6	....	50	9.9	....	24	5.8	....	48	3.0	....	45	3.6
6	....	60	1.7	....	71	7.3	....	54	4.3	....	29	6.0	....	48	2.1	....	49	4.3
8	....	62	2.1	....	74	4.9	3.88	55	3.0	....	..	4.8	....	50	1.3	....	50	1.8
10	....	..	0.8	....	75	4.4	....	..	1.5	3.50	30	1.1	....	.	1.0	3.80	49	0.7
12	5.02	59	1.4	....	..	4.0	....	..	...	....	..	...	3.76	51	1.2	....	..	...
14	....	..	...	....	74	3.6	....	..	...	....	..	...	....	..	...	....	..	...
16	....	..	...	4.90	76	2.2	....	..	...	....	..	...	....	..	...	....	..	...

* For the sake of brevity only the bidaily data are recorded. The periods are consecutive.

† In case 2 the studies were made on the same patient as in case 1, but when the concentration of hemoglobin was at a higher level.

‡ In case 6 a ten day period with 1 Gm. daily of crude chlorophyll, followed directly after the second period with pheophytin. A similar and further rise of the hemoglobin content (7 per cent) and a reticulocyte response took place.

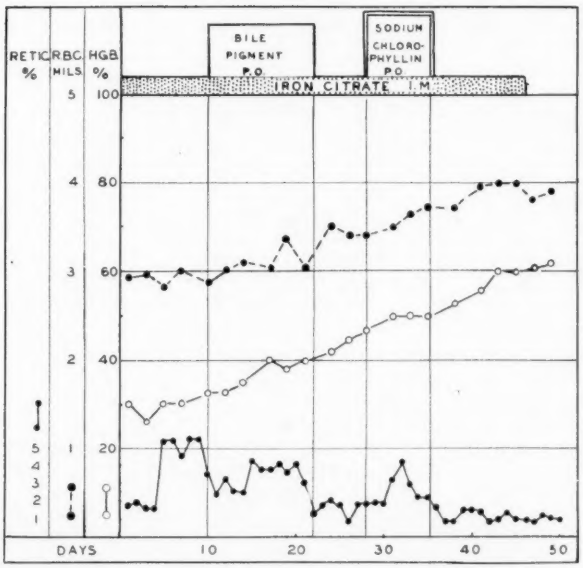


Chart 1.—Changes in the blood in a case of chronic hypochromic anemia following the administration of iron, bile pigment and sodium chlorophyllin. Note that bile pigment, a related pigment substance, behaves similarly to the chlorophyll derivatives.

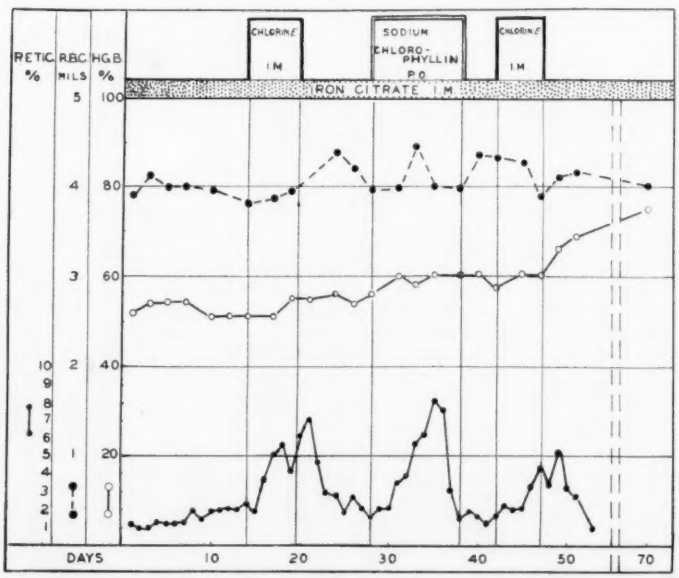


Chart 2.—Changes in the blood in a case of chronic hypochromic anemia following the administration of chlorophyll derivatives and iron. Iron citrate and chlorin *e* were given intramuscularly and sodium chlorophyllin orally.

C. Comparable Amounts of Chlorophyll and Iron (Administered Orally).—In seven series of studies on five patients ferric ammonium citrate in suboptimal doses was given daily for at least ten days, during which the usual response of reticulocytes occurred, with the peak between the fifth and the eighth days. Iron medication was continued, and a chlorophyll product was added in daily amounts comparable by weight to the dose of ferric ammonium citrate. In all instances a second reticulocyte response occurred, with the peak on about the fifth day. There were three trials with crude chlorophyll, two with pheophytin and two with sodium chlorophyllin. During the first period of about ten days with iron alone, the average percentage gain in concentration of hemoglobin was 4.6 per cent, and during the second period, 7.8 per cent. These figures allow only a rough estimate of the gain in concentration. In short intervals there may be a lag of response, so that one period overlaps the succeeding period. However, it appears that the rate of increase of concentration of hemoglobin with iron and chlorophyll therapy

TABLE 2.—*Analysis of the Results of Administering to Patients with Chronic Hypochromic Anemia Iron and Chlorophyll Products, Both Separately and Combined and Orally and Parenterally*

	Test Materials*	Results	Number of Observations
A.	Pheophytin alone	Negative	2
	Sodium chlorophyllin alone	Negative	2
	Chlorin *e* alone (I. m.)	Negative	1
B.	Iron and crude chlorophyll in disproportionate amounts†	Negative	3
C.‡	Iron and crude chlorophyll	Positive	3
	Iron and pheophytin	Positive	2
	Iron and sodium chlorophyllin	Positive	2
D.	Iron (I. m.) and sodium chlorophyllin	Positive	2
E.	Iron (I. m.) and chlorin *e* (I. m.)	Positive	3

* Substances were given orally unless otherwise indicated; I. m. means intramuscularly. A positive result signifies an observation in which after a test period with iron the addition of a chlorophyll product was followed by a second response of reticulocytes.

† This refers to cases in which small amounts of iron and relatively large amounts of chlorophyll were given, as mentioned in the text under observations B.

‡ The results in group C are recorded in detail in table 1; those in groups D and E are given in charts 1 and 2.

exceeds that with iron alone. The data for these observations are recorded in detail in table 1.

D. Iron Given Intramscularly with Sodium Chlorophyllin by Mouth.—In a series of studies on two patients 0.1 Gm. of iron citrate was injected intramuscularly daily for ten days. Moderate response of the reticulocytes occurred. With the identical therapy continued, sodium chlorophyllin was fed by mouth; to one patient 0.7 Gm. was administered daily for eight days, and to the other, 1 Gm. daily for six days. A second reticulocyte response took place promptly, which indicated that the combined effect was more potent than that of iron alone. These clinical observations are illustrated in charts 1 and 2.

E. Iron and Chlorin e Given Intramuscularly.—In a series of three studies on two patients iron citrate in doses of 0.1 Gm. daily was injected intramuscularly for ten days. A small reticulocyte response occurred. With this therapy continued, chlorin *e* was injected daily in doses of 5 cc. for five days. Each injection corresponded to 0.1 Gm. of the solid material. A second, sharp rise in the reticulocyte count occurred in both instances. The observations on one patient are illustrated in chart 2.

Data for the results in all the tests made with chlorophyll products are given in table 2, which is included for the sake of clarity.

COMMENT

Several possible causes may be considered to explain the ineffectiveness of chlorophyll derivatives alone. In certain cases of anemia there may exist a state of pure deficiency of iron; there may be no want of pyrrol or of pigment substances; and in such instances one would expect no benefit from chlorophyll therapy. Since the materials in crude chlorophyll and pheophytin are relatively insoluble, there would arise also the question of embarrassment of absorption from the gastro-intestinal tract. However, the soluble chlorophyllin salt administered orally and chlorin *e* administered parenterally likewise failed to affect the blood picture when given without iron. It is apparently essential, therefore, that iron be present before a chlorophyll substance can be utilized. Iron salts are involved in the formation of chlorophyll, although they do not enter into its molecular structure. Emerson [28] and Noack [29] showed that the growth of chlorophyll in plants can be controlled by the presence of iron salts. An analogous catalytic effect perhaps takes part in the formation of hemoglobin.

It is known that chlorophyll combines chemically with iron in the ratio of about 10 molecules to 1. In those cases in which there was a response to therapy this ratio was never exceeded, the highest being 9 to 1. In the cases in which there was no response, with a large excess of chlorophyll, the ratio to iron was as high as 35 to 1. It may be that in the latter cases iron was fixed or buried because of the strong affinity for chlorophyll and thus became unavailable for absorption from the gastro-intestinal tract.

In those cases in which a second reticulocyte response occurred together with an increased rate of regeneration of hemoglobin following the administration of chlorophyll derivatives and iron, the response appears to have been significant. A reticulocyte response occurs, to be sure, as the result of hemolysis, but signs of this were not observed. The significant second responses occurred on the addition to iron medication of chlorophyll, sodium chlorophyllin, pheophytin and chlorin *e*. In the latter two substances the magnesium radical is missing. In all preparations iron was present in insignificant traces. Hence it is illogical to consider that a mineral contamination of iron or magnesium is responsible for the increased hematopoiesis observed. The fact that similar phenomena occurred when material was administered parenterally excludes a change of gastro-intestinal absorption as the conditioning factor when material was given orally.

Nonspecific agents like potassium arsenite can provoke reticulocytosis. Unexplained spontaneous fluctuations in the reticulocyte count

28. Emerson, R.: Proc. Nat. Acad. Sc. **15**:281, 1929.

29. Noack, K.: Naturwissenschaften **17**:104, 1929.

also occur rarely. In the patients given chlorophyll and its derivatives, however, there was a rhythmic pattern of hematologic response. The time of onset of the response and the course taken by the reticulocyte count, the increase of concentration of hemoglobin and the improved sense of well-being were similar in all the patients in whom a response occurred. For these reasons it seems likely that the changes observed were not accidental and that the substances used provided a specific hematopoietic stimulus. Whether they acted in the intermediary stage of iron metabolism, that is, utilization of iron, or whether they acted simply in a substitutive way was not ascertained.

The study at least suggests that the human body can use preformed pyrrol substances in the building of hemoglobin. It is important to emphasize that such substances are not recommended for a therapeutic purpose. Iron therapy alone is adequate treatment in most cases of uncomplicated chronic hypochromic anemia. This study may serve to encourage the use of a diet ample in greenstuffs and protein foods, for it must be that over a long space of time favorably nutritious elements are absorbed which aid the blood reserve and which furnish building stones for the heme pigments necessary to the formation of hemoglobin.[30]

SUMMARY AND CONCLUSIONS

Twenty series of observations on fifteen cases of chronic hypochromic anemia were made with the aim of determining what effect the administration of chlorophyll products might produce on regeneration of the blood.

In five instances the administration of chlorophyll and its degradation products alone did not produce changes in the blood.

In three instances the administration of very large doses of crude chlorophyll with very small doses of iron likewise did not produce change in the blood.

In twelve sets of observations on nine cases the administration of chlorophyll products after a period of medication with comparable

30. In one patient fed 1 Gm. of sodium chlorophyllin daily for eight days a marked cutaneous photosensitivity on the dorsum of the hands, on the tip of the nose and on the lips developed on the seventh day, although hematoporphyria was not demonstrated. By avoiding exposure to sunlight for sixty days the lesions cleared. There were no systemic untoward effects.

Among other biologic functions, chlorophyll serves as an absorber of light energy to be used in photosynthesis. It is not unlikely that this patient's sensitivity was related to the medication. If so, it constitutes a danger in the use of chlorophyll for therapeutic purposes. A fuller exposition of this case is being prepared for a separate communication.

amounts of iron was followed by an orderly and significant increase in the concentration of hemoglobin and a second reticulocyte response.

This combined effect was produced when materials were given parenterally as well as orally.

The studies suggested that the body can use preformed pyrrol substances for the building of hemoglobin.

CYTOLOGIC EXAMINATION OF NASAL SMEARS OF SENSITIZED AND NONSENSITIZED PERSONS WITH NASAL SYMPTOMS

WITH SPECIAL REFERENCE TO THE EOSINOPHIL COUNT AND TO SIMULTANEOUS BLOOD COUNTS

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The local accumulation of eosinophil cells in the tissues and sputum of persons afflicted with bronchial asthma was one of the observations of long ago. At first only the fact of its occurrence was known; now it seems to be well established that it is one of the phenomena of the sensitized or allergic state. The occurrence of increased numbers of eosinophil cells in the sputum of persons with tuberculosis,[1] bronchitis [2] or bronchiectasis,[3] in gonorrheal discharge,[4] in the muscle of persons with trichinosis, in blisters produced by cantharides,[5] in the tissues of the intestinal tract and in the blood of persons with certain parasitic infestations, in carcinomatous tissue [6] and in the tissue of the pituitary gland in persons with certain disturbances of that gland is too well known to justify detailed comment. Various interpretations of this increase in the number of eosinophil cells have been given. However, since the early work on serum disease and anaphylaxis, it has become generally accepted that eosinophilia in the blood and in the tissues is characteristic during the manifestations of sensitization. Some observers have even gone so far as to express the opinion that all eosinophilia of the tissues, with the exception of the normal eosinophilia of the thymus, is the result of an allergic condition.

A preliminary report was made at the meeting of the University of Michigan Pediatric and Infectious Disease Society, Nov. 18, 1933.[12]

From the Sensitization Division of the Department of Pediatrics and Infectious Diseases, and the Student Health Service, the University of Michigan.

1. Teichmüller, W.: Centralbl. f. inn. Med. **19**:305 (April 2) 1898.
2. Grouven, C.: Ueber die eosinophilen Leukocyten der Schleimhaut des Respirationstractus, Inaug. Dissert., Bonn, C. Georgi, 1895.
3. Fuchs, E.: Deutsches Arch. f. klin. Med. **63**:427 (Aug. 18) 1899.
4. Vorbach, F.: Eosinophile Zellen bei Gonorrhoe, Inaug. Dissert., Würzburg, 1895.
5. Bettman: München. med. Wchnschr. **45**:1229 (Sept. 27) 1898.
6. Przewoski, E.: Centralbl. f. allg. Path. u. path. Anat. **7**:177 (March 15) 1896.

Our interest was awakened by the work of Huber and Koessler [7] (1922) on the pathology of asthma and that of Eyermann [8] and of Johnson and Goldstein [9] on the cytologic examination of nasal secretions of persons with hay fever and acute infections of the respiratory tract. Three years ago we began to record the differential cell counts of the nasal discharge of patients coming to the clinics for treatment of sensitization of the University Hospital and Student Health Service. We made no attempt to follow the differential counts from day to day. We were particularly interested to note in the several groups examined as a routine the frequency of the presence of eosinophil cells and the comparative number. All cell types were looked for, but the method of preparation and of securing material for examination may have been inadequate for the study of certain cell forms sometimes encountered that might show up better by the vital staining method. Wright's stain was used in all instances. Because of the large amount of mucus present it was necessary to stain the material longer than is usual for blood films.

Smears were made directly from the nostrils by means of a swab, a glass rod with a rounded end or a platinum loop or, as in most instances, by having the patient blow his nose on glazed paper or oiled silk. The material was spread thinly on glass slides or on cover slips and was stained in the same way as are blood films. From 100 to 200 cells were counted with the oil immersion lens. The cells had a tendency to gather in clumps and were often seen to stand out as reddened areas. One might search for some time, finding only here and there an eosinophil or a polymorphonuclear cell and then suddenly encounter a clump of 10 or more. With the mechanical stage one soon learns to run over the slide with considerable rapidity. In cover slip smears it may be necessary to examine more than one preparation to secure the total number, but this is unusual after one learns how the spreading should be done. It is of interest to note that in the sections of tissue studied by Huber and Koessler the eosinophil cells were usually found in nests along with other cells. Care must be taken not to mistake free nuclei of squamous epithelial cells for mononucleated leukocytes. These cells are often granular and sometimes take the eosin stain, but of course their morphologic characteristics at once differentiate them. In our counts we ignored cells other than those that belonged in the leukocyte group.

7. Huber, H. L., and Koessler, K. K.: The Pathology of Bronchial Asthma, Arch. Int. Med. **30**:689 (Dec.) 1922.

8. Eyermann, C. H.: Ann. Otol., Rhin. & Laryng. **36**:808, 1927.

9. Johnson, M. C., and Goldstein, D. W.: Allergy and the Cytologic Examination of Nasal Smears, Arch. Otolaryng. **16**:808 (Dec.) 1932.

As the majority of the patients came to the clinic because of a history or a family history of sensitization, we are unable to furnish observations on as large a nonsensitized control series as we should like. Such a control necessitates a complete examination for sensitization. Accordingly, volunteers were few. However, a satisfactory control was secured in our group with infectious colds. Our observations may be classified as follows:

1. The cytology of the nasal smears of sensitized persons free from an infectious cold.
   (*a*) Sensitization to pollen alone (hay fever).
   (*b*) Sensitization to pollen plus multiple food, epidermal and bacterial sensitization.
   (*c*) Multiple sensitization, but not to pollen.
   (*d*) Sensitization with an associated epidermal sensitization.
2. The cytology of the nasal smears of sensitized persons during the period of an infectious cold.
3. Comparative simultaneous differential counts of blood film and nasal film.

TABLE 1.—*Eosinophil Counts for Persons with Pure Hay Fever and No Other Sensitization Found by the Scratch Test*

Number of Patients	Type	Family History of Allergy	Percentage Variations in Cell Count of Nasal Smear: Polymorphonuclears	Eosinophils	Monocytes	Percentage Variations in Blood Count: Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Eosinophils	Monocytes	Basophils
8	Early.....	6	53-82	18-47	0	50-60	15-30	4-14	4-11	1-8	0
5	Late.....	5	37-77	23-63	0-1	56-60	19-24	6-13	4-11	3-5	0
6	Combined early and late.....	6	9-62	38-91	0-5	58-62	18-24	5-14	4-8	2-5	0
2	Potential.....	1	37-43	57-63	0	58-62	23-23	5-8	6-8	3-3	0-1
21	All types: average.....	18	9-82	18-91	0-5	50-62	15-30	4-14	4-11	1-8	0-1

EOSINOPHIL COUNT IN NASAL SMEARS OF PATIENTS FREE FROM COLD

(*a*) *Sensitization to Pollen Alone* (*Hay Fever*).—In this group we included cases of hay fever in which no other allergy was found by the scratch test. There were 21 cases in this group (table 1). Had the patients been tested by the intradermal method doubtless other sensitizations would have been found in some of them. These cases represent 24 per cent of all the cases of hay fever observed in the preparation of this report (87). Accordingly, pure pollen sensitization is comparatively uncommon. The eosinophil cell count was between 18 and 40 per cent in 10 cases, between 42 and 68 per cent in 10 cases and 91 per cent in 1 case. The rest of the cell count was made up of polymor-

phonuclear cells. In the smears in only 3 cases were mononuclear cells found. In table 1 the data are arranged according to the type of hay fever.

(*b*) *Sensitization to Pollen (Hay Fever) Plus Multiple Food, Epidermal and Bacterial*[10] *Sensitization.*—In table 2[11] are the records of 66 patients with hay fever or potential hay fever (sensitization to pollen) associated with food, epidermal and bacterial sensitization, 45 of whom had seasonal hay fever and 21 of whom have no symptoms of hay fever but because they showed definite sensitization to pollen are classed as having potential hay fever. For the entire group the eosinophil count in the nasal smears was between 19 and 40 per cent in 21 cases and between 41 and 91 per cent in 45 cases. In the table

TABLE 2.—*Eosinophil Counts for Patients with Hay Fever (Pollen) Plus Multiple Sensitization*

Number of Patients	Variation in Age, Years	Family History of Allergy, per Cent	Type of Hay Fever	Associated Sensitization				Count on Nasal Smear					Count on Blood Smear, Eosinophils, per Cent
								Polymorphonuclears		Eosinophils		Monocytes, per Cent	
				Pollen	Food	Epidermal	Bacterial	Number	Per Cent	Number	Per Cent		
8	16-31	50	Early; average...	8	4	0	6	52	25-75	49	25-75	0	1-5 3
17	17-30	94	Late; average....	17	17	12	5	48	14-81	52	19-86	0	2-11 4.2
20	16-32	90	Combined; average	20	17	13	6	47	9-81	56	19-91	0	1-9 3.7
21	16-37	86	Potential; average	21	19	13	4	42	11-77	57	23-89	25*	1-16 5.4
66	16-37	80	Totals; average..	66	57	38	21	47	9-81	54	19-91	0	1-16 4

* This was the only instance in which a mononucleated lymphocyte-like cell was noted.

the counts are arranged in relation to the type of sensitization to hay fever, and no comment is required. Mononucleated lymphocyte-like cells were seen in a smear in only 1 case.

From the count in these two series it may be said that in definitely sensitized persons with an associated sensitization to pollen the nasal smears show an eosinophil count of 20 per cent or more (96.5 per cent of cases). Sixty-five and five-tenths per cent of all persons with sensitization to pollen had an eosinophil count of between 41 and 91 per cent.

10. These tests were made with bacterial proteins furnished by the various manufacturers of food protein. They are not disintegrated bacteria and act as bacterial vaccines.

11. Reanalysis of cases included in the preliminary report[12] and the addition of others are responsible for the change in the percentages in this report.

(*c*) *Multiple Sensitization But Not to Pollen.*—Table 3 records the clinical data on 27 patients with multiple food, epidermal and so-called bacterial sensitization but without sensitization to pollen, as determined by the scratch test. The eosinophil cell counts in the nasal smears were between 25 and 40 per cent in 6 cases, between 41 and 60 per cent in 9 cases and between 61 and 89 per cent in 12 cases. It will be seen from these figures that 77.5 per cent of the patients had an eosinophil count between 41 and 89 per cent.

TABLE 3.—*Eosinophil Counts for Patients with Multiple Sensitization But Not to Pollen*

Number of Patients	Variation in Age, Years	Family History of Allergy	Sensitization				Percentage Variations in Cell Count of Nasal Smear			Blood Eosinophils, per Cent	Complaints								
			Pollen	Food	Epidermal	Bacterial	Polymorphonuclears	Eosinophils	Mononuclears		Conjunctivitis	Dermatitis Venenata	Eczema	Gastro-Intestinal Disturbance	Headache	Nasal Polyps	Rhinitis	Urticaria	Sinusitis
6	17-33	4	0	1	1	0	30-75	25-40	0	0-5	1	..	..	1	3	..	6	1	1
9	17-44	8	0	7	5	2	30-59	41-60	24* 26*	0-3	..	..	1	3	2	..	9	2	2
12	17-33	9	0	9	8	1	11-36	61-89	14* 25*	1-21†	..	1	1	5	3	1	11	3	4

* In 2 cases only mononucleated cells were noted.
† Four per cent was noted in 1; 9 per cent in 1; 21 per cent in 2, and below 4 per cent in all the others.

(*d*) *Sensitization with an Associated Epidermal Sensitization.*—Because of the striking hypersensitivity sometimes shown by persons with a reaction to epidermal proteins it was of interest to gather from series *a*, *b* and *c* the observations on those persons showing this type of sensitization and to compare the degree of increase in the eosinophil count in the nasal smears with those of patients who did not show epidermal sensitization. There were 50. Analysis shows the eosinophil count to be between 19 and 40 per cent in 11 cases, between 41 and 60 per cent in 13 cases and between 61 and 91 per cent in 26 cases.

A comparison shows:

Percentage	Group	Eosinophil Count, per Cent
23	Pure hay fever	41 to 91
23	Hay fever plus multiple sensitization, without epidermal allergy	41 to 91
44	No sensitization to pollen and no epidermal allergy	41 to 76
78	Epidermal allergy	41 to 91

From this analysis it seems that persons with epidermal sensitization have higher eosinophil counts in the nasal smears than those without epidermal sensitization.

EOSINOPHIL COUNT IN NASAL SMEARS OF PATIENTS WITH AN INFECTIOUS COLD

We made observations on 140 persons with hay fever during the period of an infectious cold. The records of 80 of these are given in table 4, with data concerning the character of the sensitization. The records of 60 are given in table 5, in which the data are used for comparison. An analysis of the entire group shows that the eosinophil cell count in the nasal smear was between 0 and 20 per cent in 111 cases and between 21 and 32 per cent in 29 cases. This showed the great predominance of polymorphonuclears and indicated that there had been a reversal from the usual count in the nasal smears of such persons during the period of an allergic nasal disturbance. Eighty per cent of the patients with an infectious cold had an eosinophil count of 20 per

TABLE 4.—*Observations on Sensitized Persons with an Infectious Cold*

Number of Patients	Variations in Age, Years	Family History of Allergy	Sensitization				Percentage Variations in Cell Count on Nasal Smear			Eosinophil Variation in Blood, per Cent
			Pollen	Food	Epidermal	Bacterial	Polymorphonuclears	Eosinophils	Monocytes	
64	17-53	52	41	25	13	11	40-96*	4-20	1-45†	0-10‡
16	18-29	14	6	4	1	3	49-79	21-49	2-29§	1-4

* The count was 90 per cent or higher in 15 cases.
† This variation was encountered in only 21 cases.
‡ The count was above 4 per cent in 13 cases.
§ The count was 2, 26, 29, 14 and 15 per cent, respectively, in 5 cases.

cent or less, and 68 per cent had an eosinophil count of 15 per cent or less.

In our preliminary report [12] we included only a few illustrative cases in which the reversal in the cell count was noted in the same person. Since that time we have kept records of 60 patients with hay fever (table 5) and 21 allergic patients without hay fever (table 6) for whom the cytologic picture of the nasal smear during a period of an infectious cold and a period of freedom from an infectious cold were recorded. The reversal was clearly demonstrated in all of them, and it was shown that an infectious cold in an allergic person may reduce the eosinophil count in the nasal smear far below that found in an allergic person free from a common cold.

12. Cowie, D. M., and Jimenez, B.: The Value of Differential Cell Blood Counts on Nasal and Sputum Films in the Diagnosis of Conditions of the Upper Respiratory and Bronchial Tracts, Am. J. Dis. Child. **48**:224 (July) 1934.

TABLE 5.—*Eosinophil Counts on the Nasal Smears of Patients with Hay Fever During a Period of Freedom from Infectious Cold and a Period with Cold*

	Period Free from Cold		Period of Infectious Cold			Period Free from Cold		Period of Infectious Cold	
Case	Polymorphonuclears, per Cent	Eosinophils, per Cent	Polymorphonuclears, per Cent	Eosinophils, per Cent	Case	Polymorphonuclears, per Cent	Eosinophils, per Cent	Polymorphonuclears, per Cent	Eosinophils, per Cent
1	72	28	87	13	31	37	63	91	9
2	9	91	100	0	32	15	85	90	10
3	62	38	100	0	33	1	99	84	16
4	50	50	91	9	34	37	63	97	3
5	51	49	84	16	35	10	90	96	4
6	69	31	91	9	36	61	39	95	5
7	49	51	99	1	37	53	47	100	0
8	0	100	95	5	38	21	79	79	21
9	26	74	94	6	39	67	33	100	0
10	32	68	81	19	40	19	81	93	7
11	21	79	78	22	41	50	50	94	6
12	0	100	52	48	42	60	40	72	28
13	12	88	76	24	43	20	80	89	11
14	19	81	90	10	44	61	39	100	0
15	4	96	95	5	45	27	73	72	28
16	65	35	100	0	46	0	100	82	18
17	25	75	75	25	47	0	100	86	14
18	21	79	78	22	48	46	54	90	10
19	66	34	100	0	49	60	40	100	0
20	42	58	88	12	50	34	66	85	12
21	10	90	100	0	51	27	76	97	3
22	82	19	100	0	52	8	92	90	10
23	21	79	100	0	53	36	64	99	1
24	44	56	87	13	54	0	100	98	2
25	55	45	87	13	55	12	88	84	16
26	22	78	74	26	56	39	60	74	26
27	39	61	79	21	57	21	79	100	0
28	2	98	98	2	58	30	70	94	6
29	25	75	100	0	59	28	72	76	24
30	27	73	75	25	60	37	63	79	21

TABLE 6.—*Eosinophil Counts on the Nasal Smears of Allergic Persons Not Sensitive to Pollen With and Without an Infectious Cold*

	Period Free from Cold		Period of Infectious Cold			Period Free from Cold		Period of Infectious Cold	
Case	Polymorphonuclears, per Cent	Eosinophils, per Cent	Polymorphonuclears, per Cent	Eosinophils, per Cent	Case	Polymorphonuclears, per Cent	Eosinophils, per Cent	Polymorphonuclears, per Cent	Eosinophils, per Cent
1	33	66	86	14	12	40	60	95	5
2	62	38	100	0	13	54	46	100	0
3	50	50	91	9	14	54	46	94	6
4	39	61	79	21	15	26	74	72	28
5	36	64	87	13	16	47	53	61	34*
6	62	38	78	22	17	22	64*	95	5
7	67	33	100	0	18	10	90	98	2
8	12	88	85	15	19	64	36	85	15
9	15	85	77	23	20	60	40	79	21
10	36	64	85	15	21	34	66	74	26
11	58	42	76	24					

* The balance of the count was made up of other cells.

COMPARATIVE SIMULTANEOUS DIFFERENTIAL COUNTS ON THE BLOOD AND NASAL FILMS

We were able to make simultaneous differential blood counts on 92 sensitized patients. These counts are analyzed in table 7 from data in tables 1, 2 and 3. This analysis indicates that 46 per cent had an eosinophil count in the blood of 4 per cent or above and 18 per cent,

TABLE 7.—*Percentage of Eosinophil Cells in the Blood of Ninety-Two Sensitized Persons*

Percentage...	0	1	2	3	4	5	6	7	8	9	10	11	16	21	23
Number of patients....	6	10	16	17	16	8	2	5	4	3	1	1	1	1	1
Percentage of patients with percentages of 4, 5, 6, 7 and more.....					46.7	29.3	20.6	18.5	13	8.5	5	4	3	2	1

a count of 7 per cent or above. The highest eosinophil count in the blood was 23 per cent (table 3); the patient had a 72 per cent eosinophil count in the nasal smear.

We have been unable to trace any definite relationship between the degree of eosinophilia in the blood and that in the nasal smear. For example:

Cases	Eosinophils, Percentage	
	In Blood	In Nasal Smear
1.....	1	78
1.....	1	28
1.....	3	91
1.....	11	23
1.....	16	52
1.....	21	60
1.....	23	72

This study, however, does show that a considerable number of sensitized persons in whom we could find no parasitic cause for their allergy had a distinctly elevated eosinophil count in the blood. One of us (D. M. C.) has observed a patient for four years who has a persistent eosinophil count of between 7 and 11 per cent, with no other explanation than the determined allergy.

The well known clinical characteristics of allergic nasal mucous membrane have been frequently noted, but our observations lead us to believe that this is not a criterion on which a diagnosis must depend. In many cases of nasal disturbance in which this well known and valuable sign is not demonstrated the condition will be found to be on an allergic basis if systematic examinations of nasal smears are made. We should like to call attention to the discouragement that might easily follow first attempts at the use of this method. The cells must be clearly demonstrated. Masses of material staining red must be differentiated from nests of eosinophil cells, which are almost invariably mixed with polymorphonuclear cells or are found in the same neighborhood.

CONCLUSIONS AND SUMMARY

1. Sensitized persons with a nasal discharge have a distinct increase in the eosinophil cells in the differential count of the nasal smear.

2. It seems safe to say that an eosinophil count in a nasal smear of from 20 to 25 per cent indicates that the patient is allergic.

3. Eosinophilia occurs in the nasal smears of persons with or without allergy for pollen. It seems to be more marked in persons who have an associated epidermal sensitization.

4. During an infectious cold there is a reversal in the cytologic picture of the nasal smear of an allergic person. The eosinophil count may be reduced far below that ordinarily noted for an allergic person.

5. Comparative simultaneous differential counts on the blood smear and nasal smear do not show a definite relationship to each other.

6. Eosinophilia in the blood, sometimes of marked degree, is not uncommon in sensitized persons in whom no parasitic cause for the eosinophilia can be discovered, and this may be of long duration.

7. The practical side to the making of differential counts on nasal smears is not inconsiderable. So-called common colds, particularly if they are recurrent, may have an allergic basis (eosinophilous colds). This can often be determined by studies of nasal smears, which may indicate whether or not a prolonged sensitization study is warranted.

8. Boggy, pale nasal mucous membrane is not a reliable criterion for the diagnosis of allergic rhinitis. When present it is significant, but it is not always present.

RHEUMATIC CARDIAC DISEASE

ASSOCIATION OF ACTIVE RHEUMATIC FEVER WITH HEART FAILURE

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The pathogenesis of heart failure in rheumatic cardiac disease is a subject of some controversy. The discussion centers about the influence of two general causes of failure: first, that of some infectious process, and second, that of a mechanical factor, exertional strain. Although clinical observations seem to indicate that the infectious element is decidedly the more important,[1] the exact nature of the infection has not been adequately determined. The present investigation was undertaken to clarify this point further.[2]

The clinical material reviewed for this study included 100 consecutive cases of uncomplicated rheumatic cardiac disease with heart failure, studied in the wards of the Presbyterian Hospital prior to 1932; 75 cases of rheumatic cardiac disease and heart failure with autopsy, and 50 clinical cases of syphilitic cardiac disease with decompensation. The history, results of physical and laboratory examination and postmortem observations have been studied to determine, if possible, the relative importance of the various factors associated with the onset of decompensation.

It has been found convenient to classify the clinical cases of rheumatic cardiac disease into three categories, depending on whether the disease was active, inactive or suspected to be active. The cases of syphilitic cardiac disease occurring in an approximately similar age group were employed as controls.

The protean nature of rheumatic fever[3] makes the determination of activity difficult. In this paper, rheumatic fever has been considered to be present when two or more of the following manifestations have

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1. (*a*) Lewis, T.: Diseases of the Heart, New York, The Macmillan Company, 1933. (*b*) White, P. D.: Heart Disease, New York, The Macmillan Company, 1931. (*c*) Burwell, C. S.: The Progressive Nature of Cardiac Failure, J. A. M. A. **95**:1633 (Nov. 29) 1930.

2. While this investigation was in progress, the following study appeared dealing with the same subject: Rothschild, M. A.; Kugel, N. A., and Gross, Louis: Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovascular Disease During Various Age Periods, Am. Heart J. **9**:586, 1934.

3. Boas, E. P., and Schwartz, S. P.: Some Modes of Infection in Rheumatic Fever, Am. Heart J. **2**:375, 1927.

occurred: arthritis, pains in the joints, subcutaneous nodules, development of a heart murmur under observations, rheumatic pleurisy, pneumonia, and pericarditis, and certain cutaneous eruptions. Table 1 lists the frequency of the occurrence of these manifestations, with records of temperature, leukocytosis and response to salicylates incorporated. The specificity of these criteria has been extensively discussed in the literature.[4] In several instances, the presence of rheumatic activity seemed to be established simply by electrocardiographic evidence, without the presence of any of the other manifestations already mentioned. This is in accord with current belief.[5]

TABLE 1.—*Percentage Incidence of Rheumatic Manifestations in 144 Admissions of 100 Patients with Rheumatic Fever and in 70 Admissions of 50 Patients with Syphilis*

	Rheumatic Fever						Syphilis	
	Active		Suspected		Inactive			
Manifestation	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number
Electrocardiographic changes*	24	34	4	5	..	..	25	18
Rheumatic fever before admission	11	17	<1	1	..	..	..	..
Subcutaneous nodules	<1	1	..	..	..	..	..	..
Arthritis	7	10	1	2	..	..	..	..
Development of heart murmur	7	10	4	6	..	..	..	..
Pericardial friction rub	13	18	1	1	..	..	4	3
Pleural friction rub	7	10	1	2	..	..	4	3
Transient pneumonia	4	5	..	..	..	..	..	..
Active lesions at postmortem examination	9	13	1†	2†	..	..	..	..
Chorea (?)	..	..	<1	1	..	..	..	..
Miscellaneous	2	3	5	7	..	..	..	..
Leukocyte count more than 11,000 per cubic millimeter of blood	32	47	15	21	Not recorded		60	42
Temperature more than 100 F. (rectal)	32	47	13	19			26	18
Response to salicylates	21	30	4	5			0	0

* Prolongation of the PR interval and also intraventricular block.
† Only one active focus one year after admission.

In this series, in a number of cases in which the disease was considered active, the patient did not present clinically the necessary criteria just listed. These have been classified as instances of "suspected" active

4. (*a*) Coburn, A.: Rheumatic Infection and the Rheumatic State, Baltimore, Williams and Wilkins Company, 1932. (*b*) Rolly, F.: Der akute Gelenkrheumatismus, Berlin, Julius Springer, 1920. (*c*) Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, Medicine **7**:383, 1928. (*d*) Clawson, B. I.: The Aschoff Nodule, Arch. Path. **8**:664 (Oct.) 1929.

5. Peabody, F. W.: Heart-Block Associated with Infectious Diseases, Arch. Int. Med. **5**:252 (March) 1910. Parkinson, J.; Gosse, A. H., and Gunson, E. B.: Heart and Its Rhythms in Acute Rheumatism, Quart. J. Med. **13**:363, 1920. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**:1, 1924. Levy, R., and Turner, K.: Impaired Auriculoventricular Conduction in Rheumatic Fever, Arch. Int. Med. **43**:267 (Feb.) 1929. Oppenheimer, B., and Rothschild, Marcus A.: Electrocardiographic Changes Associated with Myocardial Changes, J. A. M. A. **69**:429 (April 11) 1917.

rheumatic fever. For example, a transient friction rub over the precordium without other confirmatory signs led one to suspect active rheumatic cardiac disease but did not establish its presence (table 1). In many cases, no evidence of active rheumatic fever could be found. In most of these cases, in fact, there was no clue to any factor associated with decompensation. While the patients with syphilis were free from active rheumatic fever, it is of interest that several of the manifestations of rheumatic fever appeared, such as electrocardiographic changes, transient friction rub, etc. (table 1). The complete clinical picture, however, prevented any confusion with rheumatic fever.[6]

The age group represented by the patients with rheumatic fever ranged from 5 to 69, with a median age of 31. The patients with syphilis were between the ages of 26 and 71, with a median age of 46.

TABLE 2.—*Percentage Incidence of Mechanical Factors in 144 Admissions of 100 Patients with Rheumatic Fever and in 70 Admissions of 50 Patients with Syphilis*

Factor	Rheumatic Fever						Syphilis	
	Active		Suspected		Inactive			
	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number
Exercise or work	<1?	1?	<1	1	1	2	4*	3*
"Worry"	1	2	..	..	<1	1	3*	2*
Pregnancy	..	..	..	..	5	7	..	..
Cessation of digitalis	..	..	..	..	<1	1	..	..
Convulsions	..	..	..	..	<1	1	..	..
"Asthma"	..	..	..	..	..	..	1	1
Aneurysm	..	..	..	..	..	..	3	2

*The common cold was also present.

The sex distribution was unequal, females preponderating in the series with rheumatic fever and males in that with syphilis. The incidence of active rheumatic fever seemed slightly higher in the younger age groups.

In the series of clinical cases of rheumatic cardiac disease with decompensation active rheumatic fever was demonstrable in 45 per cent. In 34 per cent there was no evidence of an active process. The remaining 21 per cent were suspected of being instances of active rheumatic fever, according to the aforementioned criteria. The combined group of cases of active and suspected active rheumatic fever comprised 66 per cent of the entire series. Some mechanical strain, such as exertion, pregnancy, etc. (table 2), as the sole factor associated with decompensation was found in only 8 per cent of the cases. No significant factor could be found in 26 per cent. In the series of patients who came to autopsy the percentages correspond to those for the patients not coming

6. Juster, I. R., and Pardee, H. E. B.: Abnormal Electrocardiograms in Patients with Syphilitic Aortitis, Am. Heart J. **5**:85, 1929. Coombs, C. F.: Syphilis of the Heart and Great Vessels, Lancet **2**:227, 281 and 333, 1930.

to autopsy. Sixty-six per cent of the patients showed macroscopic and microscopic changes indicative of active rheumatic fever.

A high incidence of infection of the upper respiratory tract was found in the cases of rheumatic cardiac disease. In fact, this type of infection was the only factor of importance, other than active rheumatism, found accompanying heart failure in 45 per cent of these cases. Table 3 shows the percentage incidence of the common cold, bronchitis, etc. There was a similar magnitude of incidence of this type of infection in the cases of syphilitic cardiac disease, making it difficult to determine the exact rôle of this factor. This point will be considered later in the article.

The results in the cases of syphilitic cardiac disease were as follows: In 7 per cent there was a mechanical factor; in 45 per cent, no obvious

TABLE 3.—*Percentage Incidence of Infection of Respiratory Tract in 144 Admissions of 100 Patients with Rheumatic Fever and in 70 Admissions of 50 Patients with Syphilis*

Infection	Rheumatic Fever						Syphilis	
	Active		Suspected		Inactive			
	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number
Common cold	13	18	5	7	5	7	24	17
"Grip"	..	..	<1	1	..	..	..	..
Bronchitis	<1	1	6	8	..	..	3	2
"Cough" prior to decompensation	5	7	4	6	<1	1	13	9
"Cough" following decompensation	4	6	1	2	2	3	10	7
Chronic tonsillitis	..	..	2	3	..	..	..	..
"Sore throat" *	17	25	<1 (?)	4	..	..	..	..
Pneumonia	..	..	..	..	<1	1	1	1

*Preceding the onset of an acute rheumatic episode.

factor, and in the remaining 48 per cent, an infectious element, which in this series was an infection of the upper respiratory tract.

COMMENT

The results of this study indicate a significant relationship between active rheumatic fever and heart failure in patients with rheumatic cardiac disease. Under these circumstances, the remarkable recovery and the prolonged period of well-being after decompensation of severe degree in patients with rheumatic cardiac disease becomes understandable. Furthermore, presuming that an infection of the upper respiratory tract introduces active rheumatism, one is able to comprehend "buttonhole" mitral stenosis perfectly compensated for even in strenuous activity until, for example, a common cold is contracted, at which point heart failure suddenly sets in.[7]

7. Scarlett, E. P.: The Significance of Infection in Cardio-Vascular Disease, Canad. M. A. J. **26**:562, 1932.

Similarly, the greatest number of patients with rheumatic cardiac disease and decompensation are admitted to the hospital at the peaks of incidence of rheumatic fever in New York City.[4a] The significance of this observation, however, must be tested by a larger series of observations.

The exact rôle that infection in the upper respiratory tract plays in decompensation is a topic for speculation. The equal frequency of occurrence of such infection in both patients with rheumatism and those with syphilis makes one wonder which came first, the infection or the decompensation. The omission of definite statements in respect to this

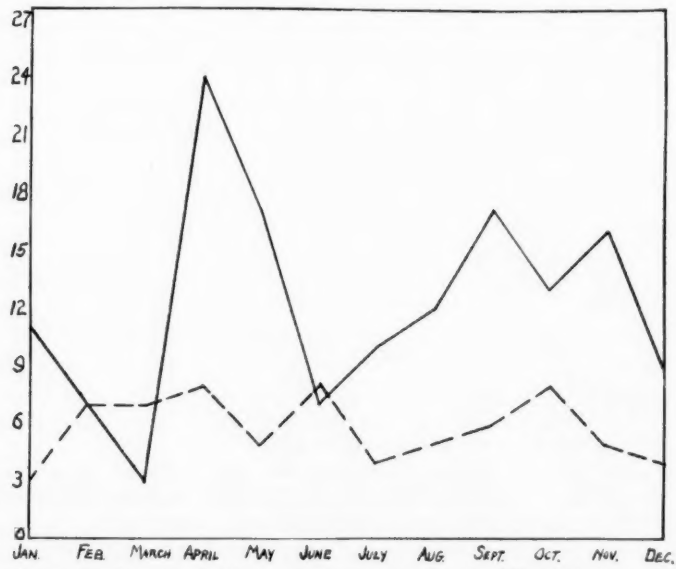

Chart showing the incidence of decompensation in 144 admissions of 100 patients with rheumatic fever and in 70 admissions of 50 patients with syphilis. The figures at the left indicate the number of admissions. The black line indicates the patients with rheumatic fever, and the broken line, the patients with syphilis.

point in the cases reported and the insidious onset of the symptoms of decompensation in the vast majority of cases preclude any definite estimate of relationships in regard to time. But the importance of infection in the upper respiratory tract as a factor in producing decompensation is understandable if one considers such infection as introducing active rheumatic fever.[8] There is, however, no myocardial process with

8. Boas and Schwartz.[3] Coburn.[4a] Branson, W. P. S.: Avenues of Rheumatic Infection, Brit. M. J. **2**:1429, 1912. McCulloch, H., and Irvine-Jones, E.: The Rôle of Infection in Rheumatic Children, Am. J. Dis. Child. **37**:252 (Feb.) 1929.

which the infection of the respiratory tract can be correlated in syphilitic cardiac disease. Thus, while the incidence of this type of infection is approximately equal in patients with syphilis and those with rheumatic fever, the occurrence of such an infection must have a different significance in the two groups.

The importance of infection in general in producing decompensation is not new to the literature. Lewis [1a] only recently again condemned the overemphasis of older views on the effect of strain in the production of heart failure (as opposed to infection). White [1b] upheld the importance of the mechanical element, claiming that the pendulum is swinging too far toward the infectious side. Burwell [1c] found that "neither the severity nor duration of overwork corresponds with the degree or time of onset of failure." The bulk of recent published opinion agrees with the latter view. In respect to the cases of rheumatism, the present study supports the opinion that it is not only infection but a specific active rheumatic infection that is the important factor in the production of heart failure.

SUMMARY

A study has been made of 100 consecutive cases of rheumatic cardiac disease with heart failure studied in wards; of 75 cases of the same condition with autopsy, and of 50 cases of syphilitic cardiac disease included for comparative purposes.

Signs of active rheumatic fever have been demonstrated in 45 per cent of the clinical cases of rheumatic cardiac disease. Activity has been suspected in an additional 21 per cent.

In the pathologic material, active lesions have been found in 66 per cent of the cases of rheumatic cardiac disease.

An exertional or mechanical factor associated with cardiac insufficiency was definite in only 8 per cent of the cases of rheumatic cardiac disease and 7 per cent of the cases of syphilitic cardiac disease. There was no demonstrable factor in the remaining 26 per cent and 48 per cent of the cases of rheumatic and syphilitic cardiac disease, respectively.

Infection of the respiratory tract is concomitant with the loss of cardiac reserve in 50 per cent of the clinical cases of rheumatic and syphilitic cardiac disease.

A seasonal rise in the number of patients with rheumatic fever admitted to the hospital for cardiac insufficiency is indicated, corresponding to the known statistics on morbidity for rheumatic fever in New York City. The finding is not demonstrable in the series with syphilitic cardiac disease.

CLINICAL STUDIES OF RESPIRATION

V. RELATION OF DYSPNEA AND AIR HUNGER TO CHANGES OF THE EXPIRATORY VOLUME OF THE CHEST

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The cause of cardiac dyspnea and air hunger is still disputed. The fact that it cannot be explained simply by alteration of the carbon dioxide and oxygen content of the blood [1] opens the way for renewed investigation of other respiratory factors.

Greene and Coggeshall [2] showed that increases in the expiratory position of the chest take place in normal subjects during muscular work and while basal metabolism is being measured. Two of their subjects who manifested such an increase also experienced shortness of breath, but when one of us (J. A. G.) [3] exposed normal subjects to high concentrations of carbon dioxide and low concentrations of oxygen, both simultaneously and separately, a constant increase in the expiratory position of the chest did not occur. In these experiments precautions were taken to reduce psychic factors to a minimum.[2]

From the Department of Internal Medicine, State University of Iowa Medical School.

1. (*a*) Peters, J. P., and Barr, D. P.: The Carbon Dioxide Absorption Curve and the Carbon Dioxide Tension of the Blood in Cardiac Dyspnea, J. Biol. Chem. **45**:537 (Feb.) 1921. (*b*) Eppinger, H.; Kisch, F., and Schwarz, H.: Das Versagen des Kreislaufes, Berlin, Julius Springer, 1927, p. 43. (*c*) Fraser, F. R.; Harris, C. F.; Hilton, R., and Linder, G. C.: Arterial Carbon Dioxide Pressure in Cardiac Dyspnea, Quart. J. Med. **22**:1 (Oct.) 1928. (*d*) Cullen, G. E.; Harrison, T. R.; Calhoun, J. A.; Wilkins, W. E., and Tims, M. M.: Studies in Congestive Heart Failure: XIII. The Relation of Dyspnea of Exertion to the O_2 Saturation and Acid-Base Condition of the Blood, J. Clin. Investigation **10**:807 (Oct.) 1931.

2. Greene, J. A., and Coggeshall, H. C.: Clinical Studies of Respiration: I. Plethysmorgraphic Study of Quiet Breathing and of Some Ordinary Activities on the Expiratory Position of the Chest in Man, Arch. Int. Med. **52**:44 (July) 1933; II. Influence of Determination of Basal Metabolism on Respiratory Movements and Effect of These Alterations on Calculated Basal Metabolic Rate, ibid. **52**:226 (Aug.) 1933.

3. Greene, J. A.: Clinical Studies of Respiration: III. Influence on the Expiratory Position of the Chest in Man of an Inspired Air Which Is Low in Oxygen and High in Carbon Dioxide and of Resistance to Inspiration and to Expiration, Arch. Int. Med. **52**:447 (Sept.) 1933.

The purpose of the present investigation was to study the effect of excess of carbon dioxide and deficiency of oxygen in patients with cardiac disease, particularly with reference to the expiratory position of the chest, and to ascertain whether or not there is any relationship between an increase in the expiratory position of the chest and air hunger and dyspnea.

METHOD

The method of altering the composition of the inspired air and obtaining simultaneous spirograms and plethysmograms was the same as that previously employed.[3] It is a procedure which reduces psychic factors to a minimum. The Haldane method of analysis of gas was used. In each case preliminary observations were made to accustom the patient to the procedure.

Of the twenty patients studied, there were four with neurocirculatory asthenia, one with pernicious anemia, two with extracardial murmurs and thirteen with organic cardiac disease. The last group included two without heart failure, six with slight congestive failure and five with advanced congestive failure. Five of the twenty patients had orthopnea, and nine experienced dyspnea on slight exertion.

RESULTS

The sensitivity of seventeen of the patients to alteration in the composition of the inspired air was within the limits designated as normal by Schneider and Treusdell,[4] Peabody [5] and Greene.[3] The carbon dioxide content of the inspired air varied from 4.2 to 10.4 per cent, and the oxygen content, from 5.6 to 10.3 per cent. The simultaneous excess of carbon dioxide and deficiency of oxygen ranged from 4.9 and 12.8 per cent to 7.5 and 9.1 per cent, respectively. Patient 14 (table 1) was abnormally sensitive; he did not experience discomfort during control periods but became short of breath when the concentration of carbon dioxide was increased to 4 and 4.5 per cent and when that of oxygen was decreased to 14.7 and 14 per cent. The result in the case of patient 17 (table 1), who was suffering from advanced congestive failure, was open to criticism; his discomfort was the same in both the control and the test period. The patient with pernicious anemia, patient 1 (table 1), became very short of breath when the content of oxygen was reduced to 11 per cent.

Table 2 shows that expiratory enlargement of the chest occurred [1a] in less than one fourth of the experiments on normal subjects,[1b] in

4. Schneider, E. C., and Treusdell, D.: A Study of Low Oxygen Effects During Re-Breathing, Am. J. Physiol. **55**:223 (March) 1921; The Effects on the Circulation and Respirations of an Increase in Carbon Dioxide Content of the Blood in Man, ibid. **63**:155 (Dec.) 1922.

5. Peabody, F. W.: Clinical Studies of Respiration: I. The Effect of Carbon Dioxide in the Inspired Air on Patients with Cardiac Disease, Arch. Int. Med. **16**:846 (Nov.) 1915.

TABLE 1.—*Reaction of Twenty Patients to Alterations in the Composition of Inspired Air*

Patient	Diagnosis	Carbon Dioxide			Oxygen			Carbon Dioxide and Oxygen			
		Percentage	Air Hunger	Expiratory Position	Percentage	Air Hunger	Expiratory Position of Chest	Percentage Carbon Dioxide	Percentage Oxygen	Air Hunger	Expiratory Position
1	Pernicious anemia; dyspnea on exertion	4.4	0	No change	11.1	Marked	Moderate increase	4.5	14.8	Moderate	Slight
2	Extracardial murmur	5.2	0	Slight increase	6.3	0	No change				
3	Extracardial murmur	5.9	0	Moderate	5.6 6.0	0 0	Slight Marked				
4	Neurocirculatory asthenia; palpitation	5.1	0	No change	8.0	0	No change				
5	Neurocirculatory asthenia; palpitation	6.1	Slight	Very slight	6.2	Slight	Very slight				
6	Neurocirculatory asthenia; dyspnea on exertion	7.2 6.6	Marked Marked	Marked Marked	6.9 9.9	Marked Marked	Marked Marked				
7	Neurocirculatory asthenia; dyspnea on exertion	5.5	Moderate	Moderate	7.1	Marked	Very slight				
8	Mitral and aortic stenosis (rheumatic) without heart failure	...	.....	.....	7.8	0	Slight	6.8	9.8	0	No change
9	Congenital cardiac disease without failure	5.7	0	No change	9.8	0	No change				
10	Mitral stenosis (rheumatic); dyspnea on exertion	5.8	0	Moderate	6.9	Moderate	Marked				
11	Arteriosclerosis; dyspnea on exertion	6.0	0	Moderate	7.9	0	No change				
12	Arteriosclerosis; dyspnea on exertion	5.5	0	Moderate	5.9	0	Slight				
13	Aortic stenosis; rheumatic; dyspnea on exertion	5.3	0	Slight	7.6	0	No change				
14	Mitral stenosis; rheumatic; dyspnea on exertion	4.0 4.5	Marked Marked	Marked Marked	14.7 14.0	Marked Marked	Marked Marked	5.0	18.0	Marked	Marked
15	Hyperthyroidism; dyspnea on exertion	5.0	0	No change	8.7 14.1	0 Moderate	No change No change				
16	Arteriosclerosis; orthopnea	5.4	0	Very slight	6.9	0	Very slight				
17	Arteriosclerosis; orthopnea; Cheyne-Stokes respiration	4.0	?	Slight	16.0	?	Slight				
18	Arteriosclerosis; orthopnea; Cheyne-Stokes respiration	5.0 4.2	0 0	No change Moderate	9.6 10.3	0 0	Moderate Moderate				
19	Arteriosclerosis; slight orthopnea	10.4	Slight	Moderate to marked	8.4	0	Moderate	7.5	9.1	0	Marked
20	Arteriosclerosis; slight orthopnea	5.8	0	Moderate	9.5	0	No change	4.9	12.8	0	No change

one half of the experiments on the various patients,[1c] simultaneously with air hunger more frequently in the patients with mild cardiac failure and neurocirculatory asthenia than in those with severe congestive failure [1d] and more frequently in patients who suffered from dyspnea on exertion than in other patients or in normal subjects. Of the fourteen patients with dyspnea on exertion, ten increased the expiratory position to a significant degree; of the six other patients only one, and of the twenty-one normal subjects only five, increased the expiratory position appreciably.

Shortness of breath without an increase of the expiratory position occurred in two instances. Patient 15 (table 1) did not experience air hunger when the content of oxygen was reduced to 8.7 per cent, but when the experiment was repeated thirty minutes later with a concentration of oxygen of 14.1 per cent she complained of shortness of breath.

TABLE 2.—*Expiratory Enlargement of the Chest in Normal Subjects and Patients*

Diagnosis	Number of Tests	Number of Instances of Increased Expiratory Position	Number of Instances of Air Hunger
Normal condition	21	5	..
Pathologic condition:			
Pernicious anemia	3	1	2
Neurocirculatory asthenia	10	5	6
Cardiac disease			
Without failure	4	0	..
With slight failure	16	9	6
With severe failure	14	7	1
Total	68	27	15

This inconsistency, together with the fact that the rate and depth of the patient's breathing increased only slightly and that she did not appear in the least short of breath, throws much doubt on the validity of the experiment. The second instance occurred in a patient with neurocirculatory asthenia, patient 7 (table 1), who appeared to be dyspneic. Just as the mouthpiece and nose-clip were being applied the patient increased the expiratory position of his chest greatly and maintained it with a slight additional increase throughout the experiment.

Definite dyspnea occurred in only five patients (table 1, patients 1, 6, 7, 14 and 19). Patients 6, 7 and 14 (table 1) exhibited dyspnea in all tests, while it occurred in patient 1 (table 1) only with a lack of oxygen and in patient 19 (table 1) only with an excess of carbon dioxide. A marked enlargement of the expiratory volume of the chest occurred in only two patients without dyspnea (table 1, patients 10 and 19). Dyspnea was accompanied by moderate air hunger in patient 10 (table 1) and was not associated with air hunger in patient 19 (table 1).

COMMENT

The variations in the sensitivity of our patients to an excess of carbon dioxide and a deficiency of oxygen compare favorably with those observed in normal subjects by Schneider and Treusdell [4] and Peabody.[5] That this variation in susceptibility is unrelated to the degree of heart failure is illustrated by the fact that patient 19 (table 1), who suffered from severe congestive failure, experienced only slight air hunger with mild dyspnea when the alveolar carbon dioxide tension was increased to 10.4 per cent by rebreathing. These results tend to confirm the conclusions of other investigators that anoxemia and acidosis caused by carbon dioxide are not the major factors in cardiac dyspnea.

If shortness of breath in cardiac disease is due partly to a reduction in vital capacity, as Peabody and Wentworth [6] and others have shown, and if an increase in the expiratory position of the chest necessarily effects a further reduction in vital capacity, it is difficult to understand why the patients with severe cardiac failure did not experience severe air hunger when the increase in expiratory position occurred, except by assuming that they were relatively insensitive to high concentrations of carbon dioxide and to low concentrations of oxygen.

The similarity of response of patients with neurocirculatory asthenia and mild heart failure suggests that in both instances the shortness of breath was produced by a reflex mechanism comparable to that which Harrison and his collaborators [7] demonstrated in their experimental study of cardiac dyspnea. The psychic factor no doubt plays a rôle in the production of dyspnea in some persons. The discovery by Levine and Wilson,[8] White [9] and Flack [10] that the vital capacity is diminished in the effort syndrome and shell shock and in aviators under "flying strain" suggests that some factor other than a mechanical one (perhaps an increase in the expiratory position of the chest) may play a rôle in the respiratory symptoms in such cases. In our patients with neurocirculatory asthenia, whose predominating symptom was shortness of breath, there was an increase in the position of the chest every time an unusual demand was made on the respiratory apparatus. This sug-

6. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of Respiration: IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917.

7. Harrison, T. R.; Harrison, W. G.; Calhoun, J. A., and Marsh, J. P.: Congestive Heart Failure: XVII. The Mechanism of Dyspnea on Exertion, Arch. Int. Med. **50**:690 (Nov.) 1932.

8. Levine, S. A., and Wilson, F. N.: Observations on the Vital Capacity of the Lungs in Cases of "Irritable Heart," Heart **7**:53 (July) 1919.

9. White, P. D.: Observations on Some Tests of Physical Fitness, Am. J. M. Sc. **159**:866 (June) 1920.

10. Flack, M.: The Respiratory Efficiency in Relation to Health and Disease, Lancet **2**:593 (Sept. 17); 637 (Sept. 24); 693 (Oct. 1) 1921.

gests that the interrelationship of the inspiratory and expiratory phases was disturbed either because of an increase in the depth of inspiration or because of a decrease in the extent of expiration. In their patients White [9] and Flack [10] found the available active expiratory power and ability to hold the breath to be reduced about 50 per cent. Observations of this kind lend plausibility to Lumsden's [11] findings that there are separate centers in the midbrain for inspiration and expiration.

Direct evidence that alterations in the expiratory or resting position of the chest are of reflex origin is to be found in the observation of Barcroft and Verzar [12] that an increase in the expiratory position occurs during the rigor produced by exposure to cold. They attributed the increase to summation of inspirations but made no mention of air hunger or dyspnea.

SUMMARY

Under conditions designed to reduce psychic influences to a minimum, the effect of raising the carbon dioxide content and lowering the oxygen content of the inspired air was studied by means of simultaneous spirograms and plethysmograms of twenty patients, thirteen of whom had organic cardiac disease, nine dyspnea on exertion and five orthopnea.

No correlation between sensitivity to such alterations in the composition of the inspired air and the degree of heart failure were discovered.

An increase in the expiratory position of the chest occurred more frequently in patients who suffered from shortness of breath on exertion than in other patients or in normal subjects.

Two thirds of the patients in whom the expiratory position of the chest increased manifested air hunger.

Definite air hunger did not occur without simultaneous increase of the expiratory position of the chest.

Definite dyspnea occurred in five patients, all of whom exhibited moderate or marked enlargement of the expiratory volume of the chest. Dyspnea did not occur in two patients with marked elevation of the expiratory level of the chest.

11. Lumsden, T.: Observations on the Respiratory Centers in the Cat, J. Physiol. **57**:153 (March) 1923; Observations on the Respiratory Centers, ibid. **57**:354 (Aug.) 1923.

12. Barcroft, J., and Verzar, F.: The Effect of Exposure to Cold on the Pulse Rate and Respirations of Man, J. Physiol. **71**:373 (April) 1931.

CARBOHYDRATE INTOLERANCE AND INTESTINAL FLORA

II. BACTERIOLOGIC STUDIES OF THE FECAL FLORA

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In another paper [1] a clinical study of sixty cases of a condition designated as intestinal intolerance of carbohydrate will be reported. This clinical syndrome characterized by flatulence, abdominal pain and belching was first described by Schmidt and Strasburger.[2] Herter [3] and Kendall [4] stated that this condition was probably due to the presence of excessive numbers of Clostridium Welchii in the intestine. Hurst and Knott [5] stated the belief that variations in the intestinal flora were not the cause of this syndrome but the result of an excess of carbohydrate in the colon due to an insufficiency of ferments.

In the present investigation, fecal specimens from persons suffering from intolerance of carbohydrate were studied bacteriologically. The study was directed primarily toward quantitative and qualitative tests for Cl. Welchii. Attempts were made to determine the diagnostic value of some of the methods suggested for routine use in the clinical laboratory.

EXPERIMENTAL METHODS

Fecal specimens were examined within three hours after collection. After mixing them to obtain a representative sample, 1 Gm. of fecal material was weighed out, carefuly emulsified in 10 cc. of sterile water and diluted so that each cubic centimeter of the suspension contained 0.01 Gm. of the original material. Liquid stools were standardized to the same turbidity as that of the weighed preparation. It is, of course, apparent that this method of preparing a "standard" suspension

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1. Althausen, T. L.; Gunnison, J. B.; Marshall, M. S., and Shipman, S. J.: Arch. Int. Med., to be published.

2. Schmidt, A., and Strasburger, J.: Experimentelle und klinische Untersuchungen über Functionsprüfung des Darmes: VI. Ueber die intestinale Gährungsdyspepsie der Erwachsenen, Deutsches Arch. f. klin. Med. **69**:570, 1901.

3. Herter, C. A.: The Influence of Food and of Epithelial Atrophy on the Manifestations of Saccharo-Butyric Intestinal Putrefaction, J. A. M. A. **49**:1965 (Dec. 14); 2077 (Dec. 21) 1907.

4. Kendall, A. I.: Intestinal Intolerance for Carbohydrate, Associated with Overgrowth of Gas Bacillus (Bacillus Welchii), J. A. M. A. **86**:737 (March 11) 1926.

5. Hurst, A. F., and Knott, F. A.: Quart. J. Med. **24**:171, 1931.

is inaccurate because of differences in water content of specimens as well as for other reasons. However, comparisons of the turbidity of a large series of such suspensions showed little variation, and no significance was attached to slight differences in results. Thus it was felt that this method was adequate for the purpose.

For quantitative estimation of Cl. Welchii, dextrose agar containing ferric chloride and sodium sulphite was prepared according to the formula of Wilson and Blair.[6] One cubic centimeter amounts of tenfold serial dilutions of fecal material of from 1 : 10 to 1 : 10,000 were plated in this medium. The plates were incubated in phosphorus jars as described by Varney.[7] Chapman [8] found a certain degree of selective action for Cl. Welchii with this method of obtaining anaerobiosis. The colonies were counted after twenty-four hours of incubation at 37 C. The counts were checked in some instances by plating measured amounts of suspension on dextrose blood agar plates.[8]

As a qualitative test for the presence of Cl. Welchii, the "stormy fermentation" of sterile milk in Smith tubes was used.[9] The standard inoculum was 1 cc. of the stock dilution, i. e., 0.01 Gm. of fecal material. Two tubes were inoculated from each specimen, one with unheated material and the other with a portion which had been heated at 80 C. for ten minutes. After twenty-four hours' incubation at 37 C. the nature of the curd, the proportion of whey expressed and the approximate amount of gas evolved were recorded.

Actual isolation and identification of Cl. Welchii were accomplished either from ferric chloride-sodium sulphite agar plates used for counts or from heated tubes of milk showing stormy fermentation. This was done by streaking the material on blood agar plates containing 2 per cent dextrose and 20 per cent blood which were incubated in phosphorus jars for forty-eight hours. Colonies of Cl. Welchii showed characteristic olive green coloration and were surrounded by a zone of hemolysis and chocolate brown precipitation as described by Zeissler.[10] The colonies were streaked again on blood plates, fished to beef heart and finally reisolated by the shake method in liver agar deeps. The type of Cl. Welchii according to Simonds' [11] classification was determined by fermentation tests of glycerin and inulin.

Qualitative tests for the presence of aciduric organisms were made according to the method used by Morris, Porter and Meyer.[12] Acetic acid was added to an extract broth containing 1 per cent dextrose so as to yield a final concentration of fifth-normal, tenth-normal and twentieth-normal acid, respectively. A tube of each concentration was inoculated with 1 cc. of the stock dilution of feces, incubated for ten days and observed for growth. Quantitative estimations of aciduric organisms were also carried out. Serial dilutions were plated in whey agar at p_H 5.6, and counts were made after forty-eight hours of incubation.

6. Wilson, W. J., and Blair, E. M. M.: J. Hyg. **24**:111, 1925.

7. Varney, P. L.: J. Lab. & Clin. Med. **11**:1183 (Sept.) 1926.

8. Chapman, G. H.: J. Bact. **16**:49, 1928.

9. Herter, C. A.: On Bacterial Processes in the Intestinal Tract in Some Cases of Advanced Anemia, with Especial Reference to Infection with B. Aerogenes Capsulatus (B. Welchii), J. Biol. Chem. **2**:1, 1906.

10. Zeissler, J.: Die Gasödeminfektionen des Menschen, in Kolle, W., and Wassermann, F.: Handbuch der pathogenen Mikroorganismen, Jena, Gustav Fischer, 1928, vol. 4, pt. 2, chap. 14, p. 1099.

11. Simonds, J. P.: Studies in Bacillus Welchii with Special Reference to Classification and to Its Relation to Diarrhea, Monogr. 5, Rockefeller Institute for Medical Research, Sept. 27, 1915.

12. Morris, G. B.; Porter, R. L., and Meyer, K. F.: J. Infect. Dis. **25**:349, 1919.

To test for the proteolytic activities of the flora, 1 cc. of serial dilutions of the unheated specimen of from 1:100 to 1:10,000,000 were inoculated into freshly boiled peptic digest beef heart medium and incubated for two weeks. Darkening and disintegration of the meat accompanied by the production of foul gas were considered to be evidence of proteolysis.

Tubes containing sterile potato mash (one part potato to six parts water) were inoculated in the same manner as the tubes containing beef heart to test the fermentative action on this substance. In addition, from 0.1 cc. to 1 cc. of potato mash was added to 10 per cent suspensions of feces. The relative amount of gas produced was recorded after twenty-four hours of incubation at 37 C.

Fecal specimens from fifty persons who presented a clinical picture of intolerance of carbohydrate were studied. Twenty-four of these persons showed typical symptoms and had no other intestinal disease; three suffered from other intestinal disorders as well, and twenty-three had symptoms suggestive of this condition but in milder form than the typical cases. It is unfortunate that only one specimen was obtained from a number of patients. However, in a series of twelve cases weekly specimens were studied over a period of from one to four months, and in two instances tests were made daily for a week. Some samples were taken during the characteristic exacerbations; others were tested during various periods of the dietary regimen.[1] As controls, seven specimens were examined from persons suffering from other intestinal diseases, three from persons with hypochromic anemia and fourteen from normal persons.

The majority of the specimens were normal in gross appearance. As a rule, they were formed and dark in color, although in ten cases they were light-colored and unformed and contained bubbles of gas. Liquid stools were submitted in only seven instances. Mucus was present in the feces of twelve patients, all of whom had severe symptoms and were refractory to treatment. Except in the cases in which mucus was found in the feces, there was no correlation of the nature of the stool either with the severity of the symptoms or with the bacteriologic findings.

RESULTS

The results of the various tests for Cl. Welchii are summarized in table 1. The detailed analyses of twenty-one specimens chosen at random are given in table 2.

Number of the Organisms Present.—It was felt that the method of quantitative estimation of Cl. Welchii gave a reasonably accurate indication of the actual number of the organisms present in the feces both in vegetative and in spore states. In ferric chloride-sodium sulphite agar colonies of Cl. Welchii were surrounded by a wide jet black zone. Although a number of other organisms produce such colonies, repeated studies of an extensive series of black colonies showed them to be Cl. Welchii with only a few exceptions. No other species of Clostridium which reduced sulphite was encountered in this series by the method used. Occasionally a streptococcus was found which formed minute black colonies readily distinguishable from Cl. Welchii. There was close agreement with counts obtained by plating on dextrose agar plates.

The counts ranged from less than 100 to as high as 250,000,000 sulphite-reducing organisms per gram of feces. Of specimens from

fourteen normal persons, three gave counts lower than 1,000, and none had a count higher than 10,000,000 organisms per gram. For eight of forty-four patients with intolerance of carbohydrate tested the counts were less than 1,000, but in eight instances they exceeded 10,000,000 organisms per gram. With the exception of this group of eight persons with counts exceeding 10,000,000 per gram, there was no evidence that the feces of those unable to tolerate carbohydrate contained any greater numbers of the organisms than did those of normal persons.

MacNeal, Latzer and Kerr,[13] Simonds,[11] Dudgeon,[14] Nye,[15] Moench, Kahn and Torrey,[16] Hines,[17] Davidson [18] and others found that Cl. Welchii may be present in considerable numbers in the feces of from 30 to 100 per cent of normal persons. In those studies in which quantitative determinations were made, the figures reported were lower

TABLE 1.—*Summary of Results of Tests for Clostridium Welchii*

	Stormy Fermentation in Milk				Count per Gram in Ferric Chloride and Sodium Sulphite Agar				
	Unheated Specimen		Specimen Heated at 80 C.			Number with Counts of			
	Number Tested	Number Positive	Number Tested	Number Positive	Number Tested	1,000	1,000 to 100,000	100,000 to 10,000,000	10,000,000
Patients with severe carbohydrate intolerance....	22	8	27	20	24	5	6	9	4
Patients with mild carbohydrate intolerance....	13	8	23	19	20	3	4	9	4
Patients with hypochromic anemia.....	3	3	3	3	3	0	1	2	0
Patients with gastrointestinal disturbances...	4	1	6	4	7	1	2	3	1
Normal persons.....	10	9	14	12	14	3	5	6	0

than those obtained in our series. For example, Nye [15] gave 240 organisms per gram as the average count for six normal persons, and the highest counts reported by MacNeal, Latzer and Kerr,[13] Hines,[17] and Simonds [11] were 39,449, 6,000 and 15,600 per gram, respectively. However, only spores were counted in the methods used by these investigators.

The count for Cl. Welchii showed absolutely no correlation with the severity of the symptoms. In fact, many of the patients with the most distressing symptoms had less than 100 of these organisms per gram of feces. An analysis of specific signs and symptoms as listed

13. MacNeal, W. J.; Latzer, L. L., and Kerr, J. E.: J. Infect. Dis. **6**:571, 1909.

14. Dudgeon, L. S.: A Study of the Intestinal Flora Under Normal and Abnormal Conditions, J. Hyg. **25**:119, 1926.

15. Nye, R. N.: J. Clin. Investigation **4**:71, 1927.

16. Moench, L. M.; Kahn, M. C., and Torrey, J. C.: Analysis of the Fecal Flora in Thirty-Three Cases of Pernicious Anemia, J. Infect. Dis. **37**:161, 1925.

17. Hines, L. E.: J. Infect. Dis. **32**:280, 1923.

18. Davidson, L. S. P.: J. Path. & Bact. **31**:557, 1928.

in the previous paper [1] showed no agreement between any of them, either alone or in combination, and the number of the organisms found. A possible exception to this statement might be the fact that of twelve patients with mucus in the stool, six had counts greater than 1,000,000 per gram. However, equally high counts were obtained for eleven patients with no mucus present.

Herter,[9] Simonds,[11] Nye,[15] Moench, Kahn and Torrey,[16] Davidson [18] and others found that patients with pernicious anemia

TABLE 2.—*Data Showing Lack of Correlation Between Various Features of the Fecal Flora*

	Aciduric Organisms			Proteolytic Organisms:	Cl. Welchii		
	Growth in Acetic Acid Broth		Count in Whey Agar, Number per Gm.	Proteolysis* in Beef Heart Medium	Stormy Fermentation in Milk		Count in Ferric Chloride and Sodium Sulphite Agar, No. per Gm.
	Fifth-Normal	Tenth-Normal			Heated (80 C.)	Unheated	
Cases of carbohydrate intolerance							
1	—	+	10,000	++	+	+	110,000,000
2	+	+	1,000	+++	+	+	1,600,000
3	—	+	200	+	+	—	1,000,000
4	—	+	800	++	—	—	<100
5	—	+	1,200,000	+++	+	—	25,000,000
6	—	+	141,000	+	—	—	<100
7	—	—	3,000	++	+	—	40,000
8	—	—	1,600	++	—	—	15,000
9	—	—	16,000	+	+	—	150,000
10	+	+	200	+++	+	+	500
11	—	+	2,500,000	+++	+	—	3,000,000
12	—	+	1,200	++	+	—	13,100
13	+	+	170,000,000	+++	—	—	<100
14	—	—	<100	+++	+	+	164,000
15	+	+	<100	+++	—	—	300
16	—	—	41,000	++	—	—	1,000
Other gastro-intestinal cases							
17	—	+	270,000	+++	—	—	<100
18	—	+	8,400	+++	—	—	<100
19	—	+	6,300	+++	+	—	30,000,000
20	—	—	13,400,000	++	+	—	1,700,000
21	+	+	3,200	+++	—	—	<100
22	—	—	700	+++	+	+	8,200,000
23	—	+	13,400,000	++	+	+	200,000

* + indicates proteolysis in dilutions up to 1:1,000; ++, proteolysis in dilutions up to 1:100,000; +++, proteolysis in dilutions up to 1:1,000,000 or higher.

almost invariably show a great numerical increase of Cl. Welchii in the intestine. It is commonly believed that the increased number of these and other organisms in a patient in this condition is due, at least in part, to the achlorhydria and the consequent altered reaction of the contents of the small intestine. In view of this, it seemed reasonable to expect that the patients in this series who showed hypochlorhydria would also harbor large numbers of these organisms. However, of twenty-one patients with a low content of gastric hydrochloric acid only five showed counts exceeding 1,000,000 per gram, whereas six of thirteen with normal gastric acidity also gave high counts.

Cl. Welchii was isolated from the feces of thirty-seven of forty-four patients unable to tolerate carbohydrate, of eight of ten patients with other disturbances and of twelve of fourteen normal persons. All the strains were strongly hemolytic, and they fermented starch both in the form of soluble starch and in potato mash. All four of Simonds' types were found, with types II and IV predominating. There was no relation between the type present and the clinical condition.

Stormy Fermentation Tests.—It can be stated that the stormy fermentation test in milk was found to be of no diagnostic value as far as this condition was concerned. As can be seen in table 1, specimens from normal persons and from those suffering from other diseases showed as large a proportion of positive results from fermentation tests as did those from patients with symptoms of intolerance of carbohydrate. The number of positive reactions as well as the degree of fermentation was greater in the heated tubes than in the unheated ones where the growth of Cl. Welchii often was inhibited, presumably by the presence of large numbers of other organisms. The quantity of inoculum was found to influence the results. When the inoculum for the unheated tubes was increased to 0.1 Gm., about 75 per cent of the specimens gave positive results regardless of their source; and with an inoculum of 0.5 Gm., every specimen tested, with the exception of one from a normal person, gave positive results.

Statements have been made by Hewes and Kendall,[19] Torrey [20] and others to the effect that stormy fermentation in milk inoculated with unheated fecal material indicates either a predominance of Cl. Welchii, or at least an abnormal number of the organisms, in the intestinal flora or else unusually reduced numbers of acidogenic bacteria. Stormy fermentation is considered by many to indicate an abnormal intestinal flora. These statements were not borne out by the data given in table 2. It even has been stated that the amount of gas in the fermentation tube is a direct index of the relative number, or even the absolute number, of the organisms present. This is obviously a fallacy since an inoculum of even a few organisms can produce maximum fermentation if conditions chance to be such that multiplication occurs. This is such an elementary point that it may seem unnecessary to stress it, but failure to appreciate it seems to have caused much confusion.

A comparison of the fermentation tests of the heated specimens with the quantitative counts showed that there was no greater effect on milk whether the inoculum contained 5 of the organisms or 100,000,000 per gram. Although in the unheated tubes as few as 5 or 10 organisms

19. Hewes, H. F., and Kendall, A. I.: The Gas Bacillus as an Agent of Intestinal Fermentation and Diarrhea, Boston M. & S. J. **166**:75, 1912.

20. Torrey, J. C.: The Fecal Flora of Typhoid Fever and Its Reaction to Various Diets, J. Infect. Dis. **16**:72, 1915.

occasionally produced fermentation, in most instances at least 100,000 or more were necessary. On the other hand, it cannot be said that negative results from fermentation tests indicate the absence of the organisms or even a low count. Fifteen of the heated specimens failed to show growth, although the counts were in several instances as high as 15,000,000 per gram, probably because the organisms were not in the spore state. Approximately 45 per cent of the unheated cultures failed to give fermentation, even though the counts ranged as high as 250,000,000.

Presence of Aciduric Organisms.—Since it has been stated by Kendall [21] and others that aciduric organisms suppress the growth and activity of Cl. Welchii in the intestine, tests were made to determine how frequently and in what numbers these organisms were present in the feces. It was hoped that the results of such tests might serve to explain the discrepancies between plate counts and stormy fermentation tests. Tubes of acetic acid broth were inoculated as a qualitative and supposedly as a roughly quantitative test for aciduric bacteria. It was found that twentieth-normal acetic acid broth was of no value since growth of nonaciduric types occurred from every specimen tested. In fifth-normal and tenth-normal acetic acid broth the proportion showing growth was approximately equal for patients with carbohydrate intolerance and for normal persons, so that the test had no diagnostic significance.

Plate counts in whey agar varied from less than 100 to as high as 800,000,000 colonies per gram. Just as in the case of Cl. Welchii, there was no correlation between the qualitative tests in acetic acid broth and the quantitative plate count. Growth sometimes occurred in fifth-normal acetic acid broth when the whey agar count was less than 100, and growth at times failed to occur when the count was as high as 20,000,000. Organisms which developed in fifth-normal and tenth-normal acetic acid broth were members of the Lactobacillus group, streptococci and occasionally yeasts.

It can be seen in table 2 that there was no agreement between the ratio of aciduric organisms to Cl. Welchii and the occurrence of stormy fermentation in milk inoculated with unheated material. Apparently fermentation of milk by Cl. Welchii may occur in the test tube in the presence of large numbers of aciduric organisms; conversely, fermentation may fail, in some instances, even when the aciduric flora is numerically negligible.

Presence of Proteolytic Organisms.—Aciduric bacteria are supposed to suppress the growth of proteolytic organisms, whereas Cl. Welchii has been said to accompany a predominantly proteolytic flora.[11] Accord-

21. Kendall, A. I.: Further Studies on the Use of the Fermentation Tube in Intestinal Bacteriology, J. Biol. Chem. **6**:257, 1909.

ingly, tests for protein-splitting organisms were made by culturing serial dilutions in beef heart medium as described.

Proteolysis occurred over a wide range of dilutions with every stool tested regardless of the character of the aerobic flora and the source of the specimen. In ten samples the digestion of the meat occurred only up to a dilution of 1 : 1,000. In all the rest there was evidence of proteolytic action of dilutions of from 1 : 10,000 to 1 : 1,000,000 or occasionally even higher. As has been aptly pointed out by Sanborn,[22] no quantitative estimate of the degree of proteolytic activity of the anaerobic organisms in the feces is possible by such methods owing, among other factors, to differences in the absolute numbers and in the variety of the aerobes present. So far as the tests go, however, there was no correlation between proteolytic activity and any other factors studied, viz., the symptoms or the count for Cl. Welchii or for aciduric organisms present.

Sanborn [22] also found that organisms capable of proteolytic action were often present in large numbers in feces in which many aciduric organisms could be demonstrated. Moreover, specimens containing only a few organisms of the aciduric group gave no greater degree of proteolysis than did samples containing millions of organisms of this type. In children, according to Morris, Porter and Meyer,[11] the absence of aciduric organisms in strongly putrefactive stools is shown by sterile acetic acid broth tubes, and marked growth in fifth-normal and tenth-normal acetic acid broth is indicative of a predominantly fermentative fecal flora. That this was not the case in the stools from adults included in this series is apparent in table 2, which shows clearly that proteolytic organisms may or may not reveal themselves in a highly diluted specimen which is capable of yielding growth in acetic acid broth.

Fermentation of Potato Mash.—Since potatoes caused distress in this series of patients more commonly than other foods, the fermentative action of the unheated fecal specimens on this starchy material was tested. No qualitative or quantitative differences were observed between the feces of those unable to tolerate carbohydrate and those of normal persons. Every specimen gave violent fermentation, often blowing the plugs out of the tubes, regardless of the amount of inoculum.

Variations in Repeated Specimens from the Same Person.—When repeated specimens from the same person were studied, there was considerable variation in the results, particularly in the qualitative tests, from day to day or from week to week. Although quantitative counts of Cl. Welchii might vary in repeated specimens, even by as much as a hundredfold, they were always consistently low or high, as the case might be, for the given person. On the other hand, in qualitative tests,

22. Sanborn, A. B.: J. Infect. Dis. **48**:541, 1931.

especially the stormy fermentation reaction, the results were extremely inconsistent. The fermentation might be present for two or three days and then suddenly disappear with little or no change in the count for Cl. Welchii or for aciduric organisms, in the diet or in the physical condition of the patient.

COMMENT

The bacteriologic studies of fecal specimens herein reported fail to reveal any etiologic relationship between Cl. Welchii and the syndrome described as intestinal intolerance of carbohydrate. There is no evidence that the feces of patients suffering from this disorder consistently contain any greater relative or absolute numbers of the organisms than do those of normal persons. Moreover, there is no reason to believe that a person harboring large numbers necessarily shows any manifestations of carbohydrate intolerance or similar gastro-intestinal disturbance. In the first place, the feces of a normal person may contain several millions of these organisms per gram. In the second place, in the cases of pernicious anemia reported by various authors [23] apparently the patients showed no signs of this condition, even though Cl. Welchii was present in the stools in enormous numbers. There seems to be no more reason to incriminate Cl. Welchii than any of the other gas-producing organisms constantly found in the intestine, although it is possible that this organism may be significant in individual cases, especially if it is multiplying in the ileum or jejunum.

The number of these organisms in the stool seems to have no relation to the number of aciduric or of proteolytic organisms found. The proportion of aciduric bacteria present apparently has no effect on the clinical condition of a person although the presence of these organisms is commonly considered to be beneficial.

It must be realized, of course, that these conclusions are based on studies of fecal specimens which in all probability do not fairly represent the intestinal flora. Simonds [11] stated the belief that the number of spores of Cl. Welchii found in the feces is a reliable index of the number of these organisms in the intestine provided that the specimens are examined within three hours after collection and that the fecal material has not remained in the colon for too long a time. However, the fecal flora probably differs greatly from that of the intestinal mucosa.

It is evident that various physiologic factors must be involved. These factors have been discussed in detail in the previous paper [1] and include the effect of diet, the upward extension of the colonic flora into the ileum and jejunum, the influence of lowered gastric acidity, the presence of increased amounts of carbohydrate in the colon and inter-

23. Herter.[3] Simonds.[11] Nye.[15] Moench, Kahm and Torrey.[16] Davidson.[18]

ference with the absorption of gas from the intestinal lumen. It is felt that the problem is as much a physiologic as a purely bacteriologic one.

Obviously, the bacteriologic possibilities have not been exhausted, and further investigation may reveal an etiologic relationship between the bacterial flora and this intestinal disturbance. Studies of the bacterial content of the small intestine would be of special value. The possible antagonistic action of Bacterium coli or other organisms on certain bacteria in the intestine should be considered. It may be significant that mucus was found in the stools of all patients who were not benefited by treatment,[1] and the relation of Clostridium Welchii and of other bacteria to the presence of mucus should be studied.

In the present state of our knowledge the clinical laboratory can be of little or no assistance in the diagnosis of this and similar intestinal disturbances. The tests carried out as a routine seem to be more misleading than helpful. This is particularly true of the stormy fermentation tests. Since the stools of nine of ten normal persons give positive results for fermentation, it can be of no diagnostic value. Even Hewes and Kendall,[19] who advocated such tests, admit that Cl. Welchii may be present in normal feces in sufficient numbers to give stormy fermentation. Moreover, the variation in results with repeated daily specimens from the same person would in itself render the test valueless.

No existent method of bacteriologic examination of the feces, no matter how elaborate and painstaking it may be, can give an accurate estimate of the extent and character of the activity of the bacteria within the intestinal tract. Hence, for the present, the diagnosis of intolerance of carbohydrate must be based entirely on clinical observations. If a particular dietary regimen affords relief to a given patient, it should be followed, regardless of whether it alters the intestinal flora as judged by reactions in the test tube.

SUMMARY AND CONCLUSIONS

Fecal specimens from persons suffering from a clinical syndrome designated as intolerance of carbohydrate were studied bacteriologically by both qualitative and quantitative methods.

The incidence of Cl. Welchii ranged from a minimum extreme of less than 100 to a maximum extreme of 250,000,000 organisms per gram. "Stormy fermentation" tests in milk were positive with the majority of specimens, without regard to the number of the organisms present. Plate counts for aciduric organisms varied from less than 100 to 800,000,000 per gram. Dilutions of specimens as high as 1:1,000 to 1:1,000,000 resulted in proteolysis when incubated in beef heart broth. Potato mash, a food causing much distress in patients, was violently fermented by all specimens in test tube cultures. Repeated

specimens from a given person often indicated a variation in flora under constant conditions nearly as great as that obtained in different persons.

These results were equally true for specimens from normal persons tested as controls.

Correlations of these results with each other indicate that: 1. The "stormy fermentation" test is not a reliable index of the presence of Cl. Welchii or of any other predominant types of organism. 2. The presence of aciduric organisms does not necessarily influence the "stormy fermentation" test, nor does their presence afford any clue as to the incidence of Cl. Welchii. 3. Proteolytic organisms occur in high frequency and in considerable numbers, without regard to the presence of aciduric types or of Cl. Welchii. 4. Violent fermentation of potato mash occurs in most specimens, without regard to evidence of intestinal symptoms.

No evidence was obtained by the fecal culture methods used in these experiments that Cl. Welchii bears any direct etiologic relationship to the clinical condition under observation. There was distinct evidence that certain tests which have been suggested for laboratory diagnosis, as well as more elaborate special tests, definitely fail to aid in diagnosis and merely cause confusion.

RENAL LESIONS IN STAPHYLOCOCCUS AUREUS INFECTIONS AND THEIR RELATION TO ACUTE GLOMERULAR NEPHRITIS

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Dyke [1] adequately studied the method of elimination of Staphylococcus through the kidneys and also the pathogenesis of the lesions produced by this organism. It was his opinion that the passage of organisms "from the blood stream to the urine occurs only as the result of the formation of lesions in the kidney substance. The steps leading to the formation of such lesions after the introduction of cocci into the blood stream appear to be something as follows: The first cocci to find their way to the kidneys are held up in the glomeruli and there destroyed. Later, coccic emboli lodge in the vessels afferent to the glomeruli; these multiply and give rise to abscesses in the cortex and boundary zone. Even before a definite abscess is established, organisms find their way through the damaged vessel walls and tubular epithelium and gain ingress to the lumina of the tubules."

Recently Rigdon, Joyner and Ricketts [2] described the lesions in the kidneys of rabbits following the intravenous injection of an exotoxin from a hemolytic strain of Staph. aureus. It was their opinion that the toxin injures the epithelial and endothelial cells of the glomerular tufts and the epithelial cells of the convoluted tubules and the loops of Henle. Any degree of injury may be found, from simple cloudy swelling to complete cellular disintegration. In the early stage the capillary loops of the tufts are dilated and filled with red blood cells, whereas later the capillaries contain few red blood cells. In the early process the endothelial cells of the tufts are swollen and a few are destroyed. Some of the glomeruli are severely injured by the toxin, as shown by the presence of desquamated cells, leukocytes and red blood cells in the capsular space, by the presence of adhesions between the tuft and the capsule and by thrombi in the capillary loops.

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1. Dyke, S. C.: On the Passage of the Staphylococcus Aureus Through the Kidney of Rabbits, J. Path. & Bact. **26**:164 (April) 1923.

2. Rigdon, R. H.; Joyner, A. L., and Ricketts, E. T.: A Study of the Action of a Filtrable Staphylococcus Toxin on the Kidney of Normal Rabbits, Am. J. Path. **10**:425 (May) 1934.

From these studies it is evident that the lesions produced in the kidney by Staph. aureus are different from those produced by an exotoxin from a hemolytic strain of Staph. aureus.

Seven patients with infection with Staph. aureus were studied to determine if there were lesions in the kidneys which correspond to those produced by bacteria and an exotoxin and if there was clinical evidence of glomerular nephritis when both types of lesions were present.

REPORT OF CASES

CASE 1.—L. R., a 28 year old white woman, was admitted to the Duke Hospital on March 1, 1933, with headache and fever. Two weeks before she had a cold and a slight hacking cough. One week previous to admission her neck "became sore," and this was accompanied by enlargement and tenderness of the lymph nodes in the cervical group on the right side.

The patient as a child was never healthy. She had measles, mumps, whooping cough and typhoid. There was no history of diphtheria, scarlet fever, pneumonia, pleurisy, rheumatic fever, or chorea. In 1918, after an attack of influenza her feet were swollen and so painful that she was unable to walk; unfortunately there was no additional information with regard to the extent and duration of this edema. In 1919 tonsillectomy was performed, and in 1924 an operation for intestinal obstruction. Several years previous to admission a rectal abscess was drained Three years before she had unilateral otitis media.

On examination the temperature was 38.2 C. (101 F.), the pulse rate 96 per minute, the respiratory rate 20 per minute and the blood pressure 115 systolic and 95 diastolic. The posterior portion of the pharynx was slightly hyperemic. The lymph nodes at the angles of the jaws were enlarged but tender only on the right. A few colonies of beta hemolytic streptococci were present in a culture of material from the throat. The white blood cell count was 9,400, and the red blood cell count was 3,500,000. The urine contained a slight trace of albumin and a few pus cells. Four days later there was an increase in the quantity of albumin in the urine and in addition red and white blood cells were present. The temperature returned to normal approximately forty-eight hours after admission. The soreness in the throat diminished, and the patient was discharged four days later.

Four days after discharge she was readmitted, with the temperature 37.8 C. (100.8 F.), the pulse rate 80 per minute, the respiratory rate 20 per minute and the blood pressure 115 systolic and 78 diastolic. A culture of material from the throat showed many colonies of alpha hemolytic streptococci and a few colonies of beta hemolytic streptococci. A large, firm red area below the angle of the mandible on the right proved to be an abscess; this was drained, and the cultures showed Staph. aureus. Approximately ten days after the operation there developed edema of the face and lower extremities, nausea and general malaise. The nonprotein nitrogen content of the blood was 43 mg. per hundred cubic centimeters, and the urine showed albumin, red and white blood cells and cellular and granular casts. The blood pressure was 160 systolic and 104 diastolic.

While in the hospital the patient acquired pain in the flanks and in the suprapubic region with burning pain on urination. Through the cystoscope the wall of the bladder was seen to be inflamed, and bloody urine spurted from both ureteral orifices. Bacillus coli was obtained in pure culture from the right kidney. A test for renal function on May 10, approximately two months after the abscess in the neck was drained, showed 18 per cent phenolsulphonphthalein excreted in the

first half hour and 8 per cent during the second half hour. The urine contained blood over a period of two months. On May 11 the blood pressure was 170 systolic and 108 diastolic, and a modified Mosenthal test gave the following results:

Time	Specific Gravity
8 a. m.	1.010
10 a. m.	1.015
12 noon	1.017
2 p. m.	1.017
4 p. m.	1.022
6 p. m.	Quantity insufficient

On May 12 the nonprotein nitrogen content of the blood was 40 mg. per hundred cubic centimeters, the refractive index 1.351 and the total protein 6.1 Gm. per hundred cubic centimeters.

The patient was last seen about two months after the onset of the illness. No information could be obtained as to her health one year later.

CASE 2.—C. B. J., a 43 year old white man, was admitted to the Duke Hospital on May 30, 1932, complaining of "pain and throbbing" in the right hip for six weeks.

At the age of 14 the patient fell and injured that hip. He remained in bed for several months, at which time the hip was incised and drained. A total of seventeen operations had been performed on the hip, the majority being for drainage.

On examination the temperature was 37 C. (98.6 F.), the pulse rate 80 per minute, the respiratory rate 18 per minute and the blood pressure 130 systolic and 90 diastolic. The right leg was 4 inches (10 cm.) shorter than the left, and the femur was rigidly fixed to the pelvis in such a position as to produce marked flexion of the thigh. There was considerable pain when the right thigh was moved. A roentgen examination showed destruction of the bone about the head of the femur and acetabulum.

On June 7 the right hip was drained; a culture of the pus showed Staph. aureus. The day after operation the temperature rose from 38.3 to 40 C. (from 101.2 to 104 F.), and it continued to be elevated until the end. On June 23 a blood culture showed Staph. aureus. The patient grew progressively worse and died on June 29.

A specimen of the urine examined on May 30 contained a trace of albumin, an occasional white blood cell and from 1 to 3 epithelial cells per high power field. Another specimen, examined on June 23, contained no albumin and only an occasional white blood cell.

Autopsy.—(Only the essential observations are recorded in all of the autopsy reports.) The right leg was from 6 to 8 cm. shorter and much smaller than the left; the latter was partially fixed in abduction. There were several scars and a recent incision in the area of the right hip. When this region was explored several sinuses and pus pockets were found and a large amount of scar tissue. The head of the right femur and the right ilium showed the characteristic lesion of chronic osteomyelitis with an acute exacerbation.

There were fibrinous adhesions between the layers of pleura on both sides of the thoracic cavity and a localized empyema on the anterior surface of the left lung. Many small abscesses were present throughout both lungs, some extend-

ing through the visceral layer of pleura. Groups of gram-positive cocci were present in the abscesses.

The heart weighed 330 Gm. Many small abscesses were found in the myocardium. The spleen weighed 340 Gm. and was an acute splenic tumor. The liver weighed 2,400 Gm. and was normal.

Both kidneys were essentially the same size. Small abscesses and a few cysts were found when the capsule was removed. There were small scars in the cortex of the kidney; mononuclear cells and a few polymorphonuclear leukocytes were present in these areas. Hyaline glomeruli were found in the scars, and usually the adjacent renal tubules were atrophic or had completely disappeared. In some glomeruli the capillary loops were filled with hyaline material, and often adhesions were present between these loops and the capsule. Sometimes Bowman's capsule was greatly thickened, resembling a hyaline membrane. Red blood cells were found in the lumens of the tubules adjacent to some of the glomeruli with adhesions. There was no evidence of inflammation in those glomerular tufts which were surrounded by red blood cells. The lumens of the tubules often contained hyaline casts in addition to red blood cells.

Cultures of the blood from the heart and of material from the sinuses in the right hip and from the pleural cavity showed Staph. aureus.

Case 3.—A. B., a 6 year old white girl, was admitted to the Duke Hospital on June 16, 1932, with a swollen left knee. The swelling was first observed three months before by a salesman when the patient was buying a pair of shoes. The knee continued to swell and became painful only one week before admission.

On examination the temperature was 40.2 C. (104.6 F.), the pulse rate 160 per minute and the respiratory rate 44 per minute. The left leg was swollen, especially about the knee and ankle. The skin over the entire extremity was red and tender. A blood culture showed Staph. aureus. The leg was incised and drained. The white blood cell count varied from 18,000 to 60,000 per cubic millimeter. The urine was normal. A septic type of temperature persisted, and death occurred four days after admission.

Autopsy.—There were two incisions approximately 6 cm. in length on the anterior surface of the left leg. The muscles in this leg were edematous and hemorrhagic; those on the lateral side of the upper third of the tibia were separated from the bone by pus. Many fibrinous adhesions were present between the layers of pleura on both sides of the thoracic cavity, and numerous abscesses were found in the viscera.

The abscesses were very diffuse in the kidneys; some apparently had their origin in the glomerular tufts. Hyaline thrombi were present in approximately 10 per cent of the glomeruli. A detailed study of the thrombi with Heidenhain's hematoxylin stain showed that they varied in size and shape and often occluded the capillary loops. The endothelial cells lining the capillaries around the thrombi could not be easily demonstrated (fig. 1). The thrombi did not show fat when stained with scarlet red, nor could fibrin and bacteria be demonstrated in them with the Goodpasture-MacCallum bacterial stain. Red blood cells in the lumens of the tubules were conspicuous in the kidney.

Case 4.—A. H. Z., a 40 year old white woman, was admitted to the Duke Hospital on Dec. 26, 1933, for a thoracoplasty for pulmonary tuberculosis. In 1928 or 1929 the patient noticed "pus in strings" in the urine on numerous occasions; this was accompanied by a high fever. There was no history of dysuria, hematuria or the passage of stones.

The urine was examined approximately once a month for the three years preceding admission to this hospital. In the voided specimens a small amount of albumin was often found and white and red blood cells. Granular casts were reported three times in the thirty-one specimens examined; however, in a catheterized specimen examined on Sept. 9, 1932, there was no albumin, casts or red blood cells, and only a few white blood cells and epithelial cells were seen.

On admission the temperature was 37 C. (98.6 F.), the pulse rate 80 per minute, the respiratory rate 18 per minute and the blood pressure 110 systolic and 66 diastolic. A roentgen examination of the chest showed an old fibrous tuberculous process in the right apex, and the entire left lung was obscured.

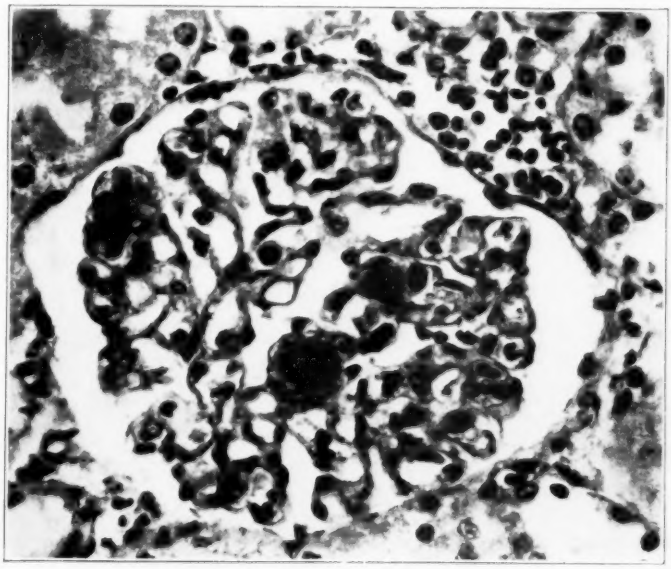

Fig. 1 (case 3).—Photomicrograph showing thrombi in the glomerulus, which seem to be formed from the necrotic and coagulated endothelial cells of the capillary loops. This lesion occurred in a child 6 years old who had acute osteomyelitis of the tibia and Staph. aureus septicemia.

probably by a thickened pleura and a tuberculous infiltration of the parenchyma. The heart and mediastinum were displaced to the left; the left side of the diaphragm was elevated to the seventh interspace, posteriorly. The white blood cell count was 10,440. The urine was normal.

The first stage of an extrapleural thoracoplasty was performed on Jan. 3, 1932. Two days after operation a culture of the wound showed Staph. aureus. The temperature reached 39 C. (102.2 F.) on the sixth postoperative day; however, it returned to normal on the fourteenth postoperative day.

Table 1 gives the specific gravity and an estimated amount of albumin in the urine during the time the patient was in the Duke Hospital. Table 2 gives the results of quantitative determinations of the albumin content (Esbach method)

from March 10 to March 16, 1934. Table 3 shows the result of Volhard concentration and water dilution tests [3] made on April 20, three and one-half months after the onset of the Staph. aureus infection in the thoracic wall.

TABLE 1.—*Specific Gravity and the Estimated Amount of Albumin in the Urine During the Time the Patient Was in the Duke Hospital*

Date	Specific Gravity	Estimated Amount of Albumin
12/30/33	1.007	0
1/ 3/34	1.013	0
1/ 4/34	1.030	0
1/10/34	1.026	1 plus
1/12/34	1.013	2 plus
1/13/34	1.028	4 plus
1/22/34	1.013	3 plus
1/31/34	1.015	3 plus
2/ 7/34	1.015	3 plus
2/21/34	1.026	3 plus
2/27/34	.....	2 plus
3/ 7/34	1.021	2 plus
3/17/34	1.022	2 plus
3/21/34	1.018	1 plus
3/28/34	1.012	trace
4/18/34	1.020	1 plus
5/ 2/34	1.023	trace
5/ 9/34	1.010	trace

TABLE 2.—*Results of Quantitative Determinations of Albumin in the Urine (Esbach's Method)*

Date, 1934	Total Amount of Urine Excreted in Twenty-Four Hours, Cc.	Gm. of Albumin Excreted in Twenty-Four Hours
3/10	1,245	1.50
3/11	570	1.14
3/12	1,660	2.15
3/13	1,685	2.86
3/14	1,395	2.50
3/15	1,580	2.60
3/16	2,140	3.40

TABLE 3.—*Results of Volhard Concentration and Water Dilution Tests*

	Patients		Controls	
Time	Amount of Urine, Cc.	Specific Gravity	Amount of Urine, Cc.	Specific Gravity
8:00 a.m.	...	.....	42	1.018
8:30 a.m.	35	1.007	250	1.001
9:00 a.m.	35	1.008	360	1.000
9:30 a.m.	175	1.001	310	1.000
10:00 a.m.	175	1.001	135	1.002
10:30 a.m.	205	1.000	...	.....
11:00 a.m.	255	1.001	65	1.010
11:30 a.m.	175	1.001	35	1.020
12:00 noon	250	1.001	20	1.020
2:00 p.m.	205	1.004	80	1.020
4:00 p.m.	50	1.012	70	1.022
6:00 p.m.	60	1.015	100	1.022
8:00 p.m.	35	1.028	105	1.026

3. The procedure is given in a book by Elywin (Nephritis, New York, The Macmillan Company, 1929, p. 33).

On May 1 the nonprotein nitrogen content of the blood was 30 mg., the urea nitrogen content 11.5 mg. and the chloride content of the plasma 484 mg. per hundred cubic centimeters. The carbon dioxide capacity was 57 volumes per cent and the refractive index 1.349; the urea clearance was 62 per cent for the first specimen and 44 per cent for the second. The patient was discharged on May 12, approximately five and one-half months after admission, with only a trace of albumin in the urine and a normal nonprotein nitrogen content of the blood.

CASE 5.—W. S., a 13 year old Negro boy, was admitted to the Duke Hospital on Nov. 6, 1933, with pain and swelling of the left ankle, forearm and wrist. Six days before admission, while standing on a chain that was suddenly jerked, he injured the left ankle. The following day there was some pain about the ankle, but he continued to walk. Two days after the accident the pain and swelling was so severe that he had to remain in bed. During this time the rate of the respirations increased, and pain developed in his chest. The pain and swelling in the forearm and wrist developed only two days before admission.

On examination the temperature was 40.5 C. (105.4 F.), the pulse rate 160 per minute, the respiratory rate 60 per minute and the blood pressure 110 systolic and 90 diastolic. There was no abrasion in the skin of the leg. A friction rub was heard on both sides of the chest and also in the precordial region. The left leg was edematous and warm. There was some tenderness about the left wrist. A culture of the blood showed Staph. aureus. The urine was normal. The patient died approximately ten hours after admission.

Autopsy.—The left leg was greatly swollen from the knee down. There was no abrasion or bruise in the skin. The subcutaneous tissues were edematous. The tissues were hemorrhagic and necrotic in the area of the interosseous septum in the lower half of the leg. The periosteum was separated from the shaft of the tibia by a large amount of pus, some of which had infiltrated into the adjacent tissues. The bone marrow in the lower third of the tibia was necrotic.

There was fresh pericarditis; the cultures showed hemolytic staphylococci (Staph. aureus). The heart weighed 190 Gm. and showed only a few small hemorrhages in the mitral valve. Both lungs were covered with a fibrinous exudate, and in section they showed many small abscesses. The liver weighed 1,130 Gm. Two small abscesses were found when the organ was sectioned.

The kidneys were swollen, and an abscess from 5 to 6 mm. in diameter was present in the cortex of the left kidney. The tubular epithelium was often swollen and necrotic, and many of the cells contained hyaline droplets. Fat was demonstrated in the tubular epithelial cells with the scarlet red stain. Red blood cells were present in the lumens of many tubules. Thrombi similar to those in case 3 were found in the afferent arterioles and in the capillaries of the glomerular tufts.

The mucosa of the colon was poorly preserved. In it were areas of necrosis and hemorrhage, and portions were covered with a diphtheritic membrane. Thrombi were present in the capillaries in the mucosa which resembled those in the capillaries of the kidney.

CASE 6.—W. R., a 26 year old white man, was admitted to the Duke Hospital on Nov. 8, 1933, with a history of a severe occipital headache for thirteen days. The patient was hit on the head with a shovel approximately two months before the onset of this headache. He was unconscious for several hours after the injury and had a headache for a few days. A dull pain in both hips and a nonproductive cough began several days before admission.

In 1922 the patient had gonorrheal urethritis which was followed by arthritis.

At the time of admission the temperature was 41 C. (105.8 F.), the pulse rate 100 per minute, the respiratory rate 24 per minute and the blood pressure 98 systolic and 64 diastolic. The heart was slightly enlarged in all diameters. A systolic murmur was heard over the precordium; this was loudest at the apex. The lungs were normal. There was slight tenderness in both lower quadrants

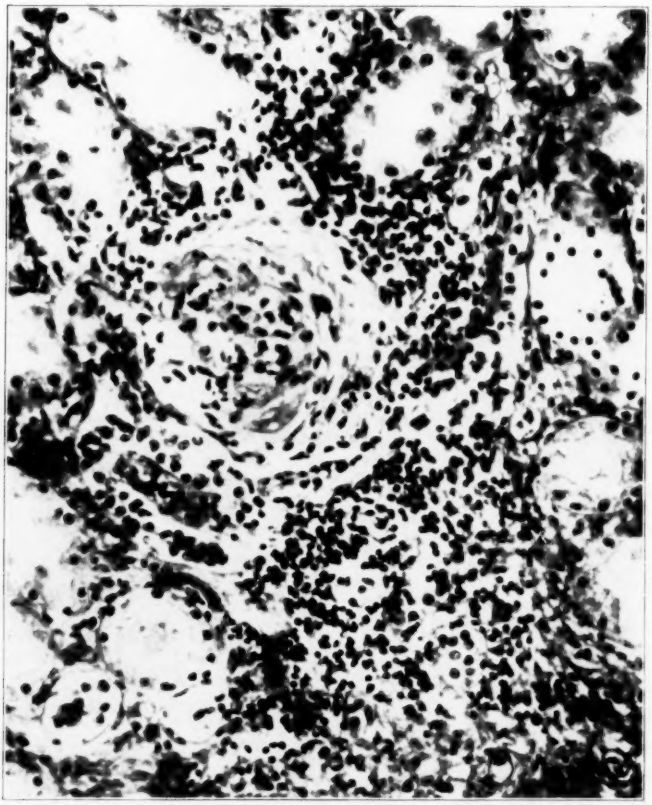

Fig. 2 (case 6).—Partial hyaline degeneration of a glomerulus with atrophy of the adjacent renal tubules and an infiltration of mononuclear cells into the area. The kidney in this case was taken from a man who had osteomyelitis of the skull, an abscess of the brain and Staph. aureus septicemia. The skull was injured approximately two and one-half months before death.

and over the sacro-iliac region on the right. The thighs were flexed and when moved caused considerable pain.

There was a small area of tenderness in the left temporal region, and a roentgen examination showed what was thought to be acute osteomyelitis of the tem-

poral bone. A culture of the blood showed Staph. aureus on the day of admission; the urine contained albumin (1 plus) and a few granular and hyaline casts. On Nov. 9, 1933, the day after admission, an abscess in the scalp was opened, a portion of the infected skull removed and an extradural abscess drained. An abscess in the right buttock was incised, and an area of infection found about the head of the right femur was drained. Cultures of material from all areas showed Staph. aureus. Twelve days after the first operation a second extradural abscess and an abscess in the temporal lobe of the brain were drained.

On November 15 the urine contained albumin (3 plus), red blood cells and white blood cells. Three days later the urine contained albumin (1 plus) and

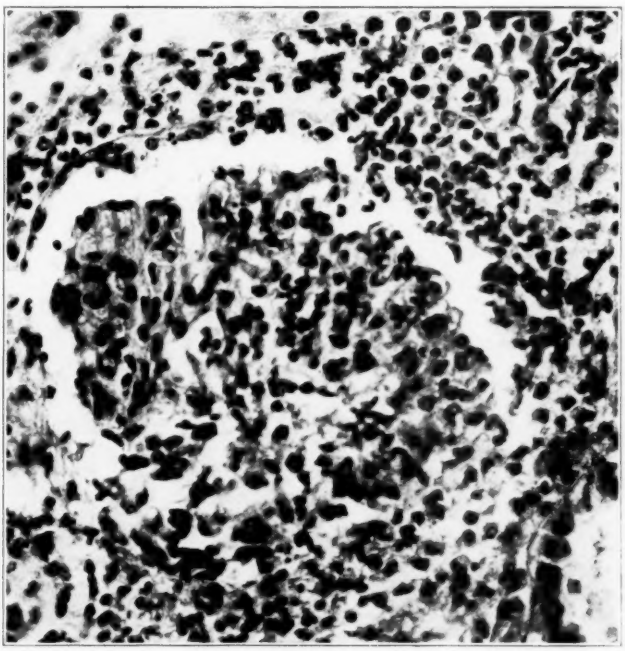

Fig. 3 (case 6).—Acute glomerulitis in a case of osteomyelitis of the skull and Staph. aureus septicemia.

10 red blood cells and innumerable white blood cells per high power field. The patient grew progressively weaker and died on November 28, twenty days after entrance.

Autopsy.—Pus could be expressed from the two incisions in the left temporal region of the scalp. There was a bony defect in the skull in this location, and the adjacent bone showed extensive necrosis. The meninges were covered with a purulent exudate. The longitudinal sinus was occluded by a thrombus, and the entering veins were dilated. Several abscesses and areas of hemorrhage were present in the cortex of the brain.

The two incisions in the skin over the right hip were infected. The head of the femur showed acute osteomyelitis. The pleura of both lungs was covered with a fibrinous exudate, and 250 cc. of thin, cloudy fluid was present in the right thoracic cavity. Abscesses were found in both lungs. The heart weighed 350 Gm., and small abscesses were present in the myocardium. There was a small friable vegetation on the mitral valve. The spleen weighed 400 Gm. and contained two large infected infarcts. The liver weighed 2,200 Gm. The thyroid gland was essentially replaced by small abscesses. There were several small superficial ulcers in the mucosa of the cecum and ascending colon, some measuring 1 cm. in

Fig. 4 (case 6).—Fibrous adhesions between the glomerular tuft and Bowman's capsule, red blood cells in the lumens of the tubules and degeneration of the renal epithelial cells in a case of osteomyelitis of the skull and Staph. aureus septicemia.

diameter. The kidneys were the same size and contained many abscesses and pinpoint hemorrhages. Numerous areas were seen in which groups of mononuclear wandering cells surrounded hyalinized glomeruli and extended down into the interstitial tissue (fig. 2). Polymorphonuclear leukocytes had infiltrated into the tuft and the capsular space and had invaded the stroma surrounding Bowman's capsule (fig. 3).

A hyalin-like thrombus occasionally occluded a capillary loop, and a few glomeruli had fibrous adhesions between the tuft and the capsule (fig. 4). The most conspicuous feature was the presence of red blood cells in the capsular

spaces and in the lumens of the tubules (fig. 5). One of the glomeruli was sectioned in such a way that the red blood cells could be seen extending from the capsular space into the neck of the renal tubules. In some instances the lumens of the tubules around these glomeruli were filled with blood casts. There were no demonstrable lesions in the majority of the tufts that were surrounded by red blood cells. In some areas the endothelial cells were necrotic in those capillary loops which contained the pink-staining material. The lesions in the glomeruli had no direct relation to the abscesses in other parts of the kidney.

Red blood cells, hyaline casts, desquamated epithelial cells and calcified casts could be found in the lumens of some of the tubules. The epithelial cells lining the tubules were often poorly preserved and sometimes contained fat.

CASE 7.—M. C., a 71 year old white woman, was admitted to the Duke Hospital on Jan. 15, 1934, for a mastectomy on the left side for carcinoma. There

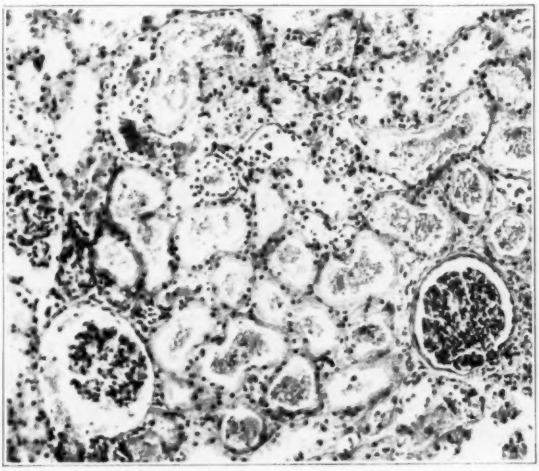

Fig. 5 (case 6).—Red blood cells are present in the capsular space of one of the glomeruli and in the lumens of the tubules. In one glomerulus the red blood cells in the capsular space are continuous with the cells in the neck of the renal tubule. This lesion was found in a case of osteomyelitis of the skull with Staph. aureus septicemia.

was nothing important in the past history except the removal of the right breast for a benign tumor ten years previously. The patient knew that she had had an elevated blood pressure for the past three or four years, but she had had no symptoms.

On examination the temperature was 37 C. (98.6 F.), the pulse rate 84 per minute, the respiratory rate 28 per minute and the blood pressure 196 systolic and 105 diastolic. The left nipple was retracted, and a firm irregular mass was palpable in the breast. On January 15 the day preceding operation, a voided specimen of urine had a specific gravity of 1.01; it was acid in reaction and showed neither sugar nor albumin; an occasional white blood cell was present, but no red blood cells or casts were noted.

At operation the left breast was removed and the axillary lymph nodes were resected. On the fourth postoperative day the patient had a chill, and the temperature reached 40.4 C. (105.1 F.). At this time a culture of material from the operative wound showed hemolytic staphylococci (Staph. aureus); a culture of the blood gave negative results, and a catheterized specimen of urine was normal.

On the eighth postoperative day the temperature was still elevated, and the wound was explored and drained. A culture of the blood gave negative results at this time, and a catheterized specimen of urine showed albumin (1 plus) with from 15 to 20 white blood cells and an occasional hyaline cast.

On January 23 the nonprotein nitrogen content of the blood was 90 mg. per hundred cubic centimeters, the chloride content (plasma) 498 mg., the uric acid content 7.7 mg., and the creatinine content 4.4 mg.; the carbon dioxide capacity was 49.8 volumes per cent. A catheterized specimen of urine showed albumin (2 plus), some red and white blood cells and blood casts. A culture of the blood showed hemolytic staphylococci (Staph. aureus) on January 26; the following day a voided specimen of urine contained albumin (1 plus), with approximately 16 white blood cells per high power field. The patient grew progressively worse and died on January 28, the fourteenth postoperative day. Autopsy was not performed.

COMMENT

The clinical picture in case 1 was characteristic of acute glomerular nephritis and resembled that in the cases with an associated streptococcic infection. A few streptococci were found in a culture of material from the throat of this patient but no more than it is usual to find in routine cultures made of material from the throat. The predominating infection was in the nodes on the right side of the neck; Staph. aureus was cultured from the abscess. Cystoscopic examination made approximately two months after the abscess in the neck was drained revealed bloody urine spurting from the orifices of both ureters. An elevation of the blood pressure and the edema of the face and lower extremities showed definitely diminished renal function. In two months the blood pressure rose from 115 systolic and 95 diastolic to 170 systolic and 108 diastolic. Over a similar period the red blood cell count dropped from 3,500,000 to 2,540,000. There was a decrease from the normal in the specific gravity with a tendency toward fixation, as shown by the Mosenthal test.

The urinary findings in case 4 supplied the only data on which a diagnosis of acute nephritis could be made. The reaction for albumin was 1 and 2 plus on the seventh and ninth postoperative days, respectively, and 4 plus on the tenth postoperative day. Albumin persisted in considerable amounts (3 and 4 plus) for approximately five weeks; afterward the amount gradually decreased. There was only a trace of albumin in the urine when the patient was discharged five months after operation.

There was an increase in the amount of albumin in the urine as estimated quantitatively (table 2). It is interesting to note that these

examinations were made when there was a decrease in the estimated amount of albumin. The data obtained from the water dilution and concentration tests indicate renal insufficiency.

Although the patient in case 7 had an elevated blood pressure before operation, there were no symptoms of renal insufficiency and the urine was normal. On the ninth postoperative day a catheterized specimen of urine showed albumin (2 plus), red blood cells and blood casts; the nonprotein nitrogen of the blood was 90 mg. per hundred cubic centimeters. It is plain that the kidney had sustained damage following an infection with a hemolytic strain of Staph. aureus.

There was nothing in the history, physical examination or laboratory findings in cases 2, 3 and 5 to suggest any renal damage. In case 6 the urine showed albumin, red blood cells and hyaline and granular casts.

The lesions in the kidneys help to interpret the clinical observation made in cases 1, 4, 6 and 7. The kidneys in all these instances had red blood cells in the lumens of the tubules. Sometimes only a few groups of tubules were involved, and in other cases the process was very diffuse. The red blood cells in the lumens of the tubules in one case were shown to have their origin from the blood in the glomerular space.

Sometimes the epithelial cells in the convoluted portion of the renal tubules were swollen and contained hyaline droplets. The lumen was dilated in this portion of the tubules; the epithelial cells were cuboidal, resembling those that MacNider [4] described as regenerated cells. Albumin, hyaline casts and red blood cells were seen in the lumens of the tubules in all the kidneys studied pathologically.

The thrombi found in capillary loops of some of the glomeruli were not "hyaline thrombi." They were apparently formed by fusion of endothelial cells which had undergone necrosis. Those thrombi did not contain either fibrin or fat; bacteria could not be demonstrated in them. Baehr [5] described similar thrombi in the kidney in the early stages of glomerular nephritis and stated that hyaline thrombi represented the healed stage of the type of thrombi found in the capillaries in these cases.

Some of the glomeruli which had thrombi in the capillaries had adhesions between the loops and Bowman's capsule. Fibrous adhesions were present between some of the tufts and Bowman's capsule in which there were no capillary thrombi. Some of the glomeruli were represented by a mass of hyaline tissue; the tubules about these glomeruli were collapsed, and the adjacent tissue was infiltrated with mononuclear cells.

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4. MacNider, W. de B.: A Pathological Study of the Naturally Acquired Chronic Nephropathy of the Dog, J. M. Research **34**:177 (May) 1916.

5. Baehr, George: Glomerular Lesions of Subacute Bacterial Endocarditis, J. Exper. Med. **15**:330 (April) 1912.

The occurrence of lesions in the kidney is not constant in staphylococcic infections. In cases of renal damage there can usually be found abscesses. The capillary thrombi and glomerular adhesions seem to be most often the result of injury produced by the staphylococcus toxin.

A marked increase in the amount of albumin and the number of red blood cells and hyaline and granular casts in the urine is found only in cases in which there has been damage to the functional unit of the kidney. The absence of edema and the presence of normal blood pressure have been observed in cases of acute glomerular nephritis due to the streptococcus. The degree of damage to the kidney in staphylococcic infections is evidently very slight; it is usually insufficient to produce an elevation in the nonprotein nitrogen content of the blood; however, this may occur, as shown by case 1.

One can readily understand why so little attention has been given to staphylococci as an etiologic agent in glomerulonephritis when the cases here are considered. The amount of blood and albumin in the urine is usually small and is present only for a short time. Evidently glomerulonephritis due to Staph. aureus occurs only rarely; however, it is suggested that some of the hyaline glomeruli found in the cases in which clinical nephritis is not present may be the result of a previous staphylococcic infection.

The etiology and pathogenesis of the lesions in the kidney may be summarized as follows: In a localized Staph. aureus infection or in a staphylococcic bacteremia the organisms produce a toxin which injures the endothelial cells. As a result of this damage the permeability of the capillary wall is increased; red blood cells escape into the glomerular space and then pass into the lumen of the tubules. If the injury is severe the endothelial cells swell, become necrotic and fuse with the adjacent cells to form the thrombi which have been described; the damaged capillary loop may become adherent to Bowman's capsule. The epithelial cells lining the renal tubules are injured by the toxin. It is impossible at this time to say whether the toxin is excreted through the glomerulus and damages the epithelium as it passes downward or whether it is brought by the blood to the epithelial cells and injures them directly.

CONCLUSIONS

Seven cases of Staph. aureus infection are reported in which there was either clinical or pathologic evidence of renal damage.

In the cases studied clinically the findings were the same as those in any case of acute glomerulonephritis.

The thrombi in the capillary loops may be the result of necrosis and fusion of endothelial cells and resemble some of the thrombi which Baehr described in the kidneys in cases of subacute bacterial endocarditis.

The presence of red blood cells in the glomerular spaces and in the lumens of the tubules is a constant finding in these cases.

Many of the lesions in the kidney resemble those produced experimentally in the rabbit by the intravenous injection of staphylococcus toxin.

AURICULOVENTRICULAR HEART BLOCK DUE TO BILATERAL BUNDLE-BRANCH LESIONS

REVIEW OF THE LITERATURE AND REPORT OF THREE CASES WITH DETAILED HISTOPATHOLOGIC STUDIES

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Lesions of the main branches of the bundle of His as a cause of auriculoventricular heart block have not been sufficiently emphasized, although this cause ranks in importance with lesions of the bundle of His itself, such as fibrosis, calcification and gummatous infiltration. The reason for the lack of recognition of the importance of this cause of heart block lies undoubtedly in the paucity of careful histopathologic studies in cases of heart block. Mahaim,[1] whose work is outstanding in this field, in completely reviewing the literature concerning histopathologic studies of the conduction system in cases of complete heart block was able to select only 25 cases, including 4 of his own, in which the studies were complete and entirely satisfactory in all respects. He selected 11 more cases the reports of which showed only insignificant defects and which could be considered relatively satisfactory. All of the other 79 cases reported were not acceptable by Mahaim because of incompleteness of the clinical data or of the histopathologic studies. We accept, however, 3 cases which Mahaim did not include in his lists of entirely or relatively satisfactory cases.[2] We have also searched the literature from Jan. 1, 1930, to the last of March 1935, the period since

From the Georgetown University School of Medicine and the Army Medical Museum.

1. Mahaim, I.: Les maladies organiques du faisceau de His-Tawara, Paris, Masson & Cie, 1931.

2. The case of Nagayo (Ztschr. f. klin. Med. **67**:495, 1909, case 1), which Mahaim lists among the paradoxical cases, should be added to this list. The case of Cohn and Lewis (Heart **4**:7, 1912), listed by Mahaim among the cases of complete heart block due to incomplete lesions, while not thoroughly studied, is also relatively satisfactory. We must also add case XI of Mahaim,[1] which he includes in his own series of cases of bundle-branch block, but which was apparently a case of complete heart block with ventricular tachycardia and right bundle-branch block (old terminology), as Mahaim himself states.

Mahaim's study, and can add only 7 cases [3] to the list.[4] Thus the total number of cases acceptable to Mahaim and to us is 48, including the first 2 cases of this report.

In order to make a complete study of the conduction system, serial sections must be made not only of the auriculoventricular node and bundle but also of both bundle branches down to the bases of the papillary muscles. Unfortunately, in man the terminal subendocardial ramifications of the branches and the intramyocardial network of the conduction system are almost impossible to recognize, although from the studies of animals it is known that such extensions exist. In many cases it may suffice to mount and stain only every twentieth section when the sections are 10 microns thick, but in some cases it is advisable to mount and stain every tenth or fifth section or even every section. In the average case 5,000 or 6,000 sections are cut. Much experience is required before one can make reliable studies and draw tenable conclusions.

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3. (*a*) Yater, W. M.: Congenital Heart-Block: Review of the Literature; Report of a Case with Incomplete Heterotaxy; the Electrocardiogram in Dextrocardia, Am. J. Dis. Child. **38**:112 (July) 1929. (*b*) Yater, W. M.; Lyon, J. A., and McNabb, P. E.: Congenital Heart Block: Review and Report of the Second Case of Complete Heart Block Studied by Serial Sections Through the Conduction System, J. A. M. A. **100**:1831 (June 10) 1933. (*c*) Yater, W. M.; Barrier, C. W., and McNabb, P. E.: Acquired Heart Block with Adams-Stokes Attacks Dependent upon a Congenital Anomaly (Persistent Ostium Primum): Report of a Case with Detailed Histopathologic Study, Ann. Int. Med. **7**:1263 (April) 1934. (*d*) Yater, W. M.; Leaman, W. G., and Cornell, V. H.: Congenital Heart Block: Report of the Third Case of Complete Heart Block Studied by Serial Section Through the Conduction System, J. A. M. A. **102**:1660 (May 19) 1934. (*e*) Grant, R. T., and Camp, P. D.: A Case of Complete Heart Block Due to an Arterial Angioma, Heart **16**:137 (July) 1932. (*f*) Don, C. S. D.; Grant, R. T., and Camp, P. D.: A Case of Complete Heart Block with Varying Ventricular Complexes, ibid **16**:145 (July) 1932. (*g*) Yater, W. M., and Cornell, V. H.: Heart Block Due to Calcareous Lesions of the Bundle of His: Review and Report of a Case with Detailed Histopathologic Study, Ann. Int. Med. **8**:777 (Jan.) 1935.

4. The case of Parade and Voit (Deutsche med. Wchnschr. **57**:629 [April 10] 1931) could probably be added if they had given the details of their histologic technic. The cases of Papp (Policlinico [sez. med.] **39**:252, 1932) and of Rosenthal (Arch. Int. Med. **50**:730 [Nov.] 1932), and the numerous ones of Géraudel and his collaborators (Ann. d'anat. path. **6**:1075 [Nov.] 1929, Paris méd. **2**:25 [July 5] 1930; Arch. d. mal. du cœur **23**:704 [Nov.] 1930; Ann. d'anat. path **8**:339 [April] 1931; Arch. d. mal. du cœur **24**:605 [Oct.] 1931; Ann. d'anat. path. **9**:715 [July] 1932; Arch. d. mal. du cœur **25**:605 [Oct.] 1932; ibid. **26**:1, 1933) cannot be included because of the apparent incompleteness of the studies. The six cases of Kung and Mobitz (Arch. f. exper. Path. u. Pharmakol. **155**:295, 1930) must be excluded also, because the details of the histologic technic are not given and the electrocardiograms are not reproduced. The case of Don, Grant and Camp [3f] is included, although the left bundle branch was apparently not completely studied: the lesion found, however, was sufficient to explain both the auriculoventricular dissociation and the varying ventricular complexes.

Mahaim [3] observed that in practically all cases of established complete heart block in which studies of the conduction system had been made and in which the latter had been pronounced by the investigator to be normal or not sufficiently diseased to produce heart block the bundle branches had not been carefully examined in their entire course. His conclusion from a study of all of the acceptable data was that established auriculoventricular heart block is always due to interruptive organic lesions of the auriculoventricular node or bundle or of both bundle branches, the latter being affected either alone or with the bundle. There are, of course, cases of transient heart block due to toxic depression of the conduction system, as in rheumatic or diphtheritic myocarditis, or to excessive vagal stimulation, as with large doses of digitalis. Géraudel [4] does not agree with this conception of the organic nature of permanent heart block since in most of his cases he did not find serious lesions of the auriculoventricular node or bundle. He did not, however, examine the bundle branches throughout their course although the electrocardiograms in several of his cases indicate that lesions of the bundle branches may have existed.

Of the 48 [5] cases of complete auriculoventricular heart block accepted by Mahaim and by us as being satisfactory from the standpoint of the histopathologic examinations and otherwise, there were 9 [6] in which the bundle branches were interrupted by organic lesions at one or several points and in which the auriculoventricular node and bundle were normal. There were other cases of auriculoventricular heart block in which there were destructive lesions of both bundle branches but in which there were also destructive lesions of the bundle of His. The accom-

5. This number includes cases 1 and 2 of this report. Case 3 is not included because the heart block was neither permanent nor complete.

6. The case of Hoffmann and Mönckeberg (Hoffmann, A.: Die Elektrokardiographie als Untersuchungsmethode des Herzens und ihre Ergebnisse, Wiesbaden, J. F. Bergmann, 1914. Mönckeberg, J. G.: Zur Einteilung und Anatomie des Adams-Stokes'schen Symptomenkomplexes, Beitr. z. path. Anat. u. z. allg. Path. **63**:99, 1916), described by Mahaim as one of bilateral bundle-branch block, is not so considered by us because the bundle of His was seriously affected as well as the bundle branches. The cases of Waldrop (Bradyarrhythmie dans une fibrillation auriculaire avec extrasystole cliniquement diagnostiquée, électro et anatomiquement ratifiée [sic]; nodule calcaire dans la branche droite du faisceau de His, Rev. Asoc. méd. Argent. **37**:74, 1924), Schmiedl (Beitrag zur Kenntnis der Adams-Stokes'schen Krankheit, Ztschr. f. Herz u. Gefässkr. **5**:393, 1913), Herxheimer and Krohl (Das Adams-Stokes'sche Symptomenkomplex und das Hissche Bündel, Deutsches Arch. f. klin. Med. **98**:330, 1910), Pletnew and Kedrowsky (Ein Fall von Morgagni-Adams-Stokes'schen Symptomenkomplex, Ztschr. f. exper. Path. u. Therap. **9**:594, 1911) and of Wenckebach and Winterberg (Die unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927, p. 349) were probably cases of heart block due to bilateral bundle-branch lesions, but they cannot be included because the reports are all lacking in some important details.

panying table shows the character and seat of involvement of the conduction system in the 48 cases of complete heart block accepted by Mahaim and by us.[8]

The Pathologic Lesions in the Forty-Eight Accepted Cases of Complete Heart Block Studied Histopathologically *

Lesion and Site	Cases
Fibrosis of the A-V* bundle with or without involvement of the bundle branches	10
Fibrosis of both bundle branches	9
Gumma of the interventricular septum destroying the A-V bundle	7
Calcium mass interrupting the A-V bundle	6
Fibrocalcareous lesion of the A-V bundle	4
Congenital cardiac anomaly with lack of continuity of the conduction system	3
Ischemic necrosis of the A-V bundle	2
Acute diphtheritic inflammation of the A-V bundle	1
Aneurysm of the interventricular septum destroying the A-V bundle	1
Separation of the A-V node from the auricular myocardium by fat	1
Tuberculous myocarditis destroying the A-V bundle	1
Primary lymphangio-endothelioma of the A-V node	1
Fibrosis of the A-V bundle in a case of persistent ostium primum	1
Arterial angioma of the right side of the septum destroying the terminal portion of the A-V bundle	1

* "A-V" represents "auriculoventricular."

7. Footnote 7 deleted by the authors.

8. In the following list the cases are distinguished by roman numerals: I. (*a*) Luce, H.: Zur Klinik und pathologischen Anatomie des Adams-Stokes'schen Symptomenkomplexes, Deutsches Arch. f. klin. Med. **74**:370, 1902. (*b*) Fahr: Ueber die muskuläre Verbindung zwischen Vorhof und Ventrikel (das Hissche Bündel) im normalen Herzen und bei Adams-Stokes'schen Symptomenkomplex, Virchows Arch. f. path. Anat. **188**:562, 1907. II. (*c*) Chapmann, W.: A Case of Cardiac Syphiloma with Bradycardia and Obstruction of the Inferior Vena Cava; the After History and a Post-Morten Examination, Lancet **2**:219, 1906. (*d*) Keith, A., and Miller, C.: Description of a Heart Showing Gummatous Infiltration of the A-V Bundle, ibid. **2**:1429, 1906. III. (*e*) Ashton, T.; Norris, G., and Lavenson, R.: Adams-Stokes' Disease Due to a Gumma in the Interventricular Septum, Am. J. M. Sc. **133**:28, 1907. IV. (*f*) Deneke, T.: Zur Roentgendiagnose seltenerer Herzleiden, Deutsches Arch. f. klin. Med. **89**:39, 1907. Fahr,[8b] V.-VI. (*g*) Bönninger: Zwei Fälle von Herzblock, Deutsche med. Wchnschr. **34**:2293, 1908. (*h*) Mönckeberg, J. G.: Untersuchungen über das Atrioventrikularbündel im menschlichen Herzen, Jena, Gustav Fischer, 1908. VII. (*i*) Volhard, F.: Ueber die Beziehung des Adams-Stokes'schen Symptomenkomplexes zum Herzblock, Deutsches Arch. f. klin. Med. **97**:348, 1909. Mönckeberg,[8h] p.120. VIII. (j) Gibson, E. A., and Ritchie, W. T.: Further Observations on Heart Block, Practitioner **78**:589, 1907; Edinburgh M. J. **1**:315, 1909; Lancet **1**:833, 1909. IX. (*k*) Pick, E.: Zur Kenntnis der Adams-Stokes'chen Krankheit, Verhandl. d. deutsch. Kong. f. inn. Med. **26**:460, 1909; **30**:511, 1913. (*l*) Koch, W.: Zur pathologischen Anatomie der Rythmusstörungen des Herzens, Berl. klin. Wchnschr. **47**:1108, 1910. X. (*m*) Nagayo, M.: Pathologisch-anatomische Beiträge zum Adams-Stokes'schen Symptomenkomplex, Ztschr. f. klin. Med. **67**: 495, 1909, case 1. XI. Volhard.[8i] (*n*) Mönckeberg, J. G.: Zur Einteilung und Anatomie des Adams-Stokes'schen Symptomenkomplexes, Beitr. z. path. Anat. u. z. allg. Path. **63**:77, 1916, p. 97. XII. (*o*) Bishop: Adams-Stokes Disease with Complete Heart Block Showing a Conspicuous Lesion in the Path of the A-V Bundle, Am. J. M. Sc. **139**:62, 1910. (*p*) Oppenheimer, Adele, and Oppen-

(Footnote continued on next page)

The following are summaries of the 7 acceptable cases of complete auriculoventricular heart block due to bilateral bundle-branch lesions among the acceptable cases of complete auriculoventricular heart block which have been reported by other authors.

1. Deneke and Fahr,[sf] 1907. A man, aged 42, had Adams-Stokes attacks for four years. Polygraphic tracings showed complete heart block with a ventricular rate of from 25 to 30 per minute. The heart was dilated, and there was diffuse myocardial fibrosis. The histopathologic study showed fibrosis involving the entire left branch at its origin and fibrosis destroying the right branch at its termination.

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heimer, B. S.: Three Cases of Adams-Stokes Syndrome, with Histological Findings, Arch. Int. Med. **13**:957 (June) 1914. XIII. (*q*) Monrad-Krohn, G.: Den atrioventriculære muskel-forbindelse i menneske hjertet (fasciculus atrioventricularis), Christiania, Steen, 1911. XIV. (*r*) Heilecker, W.: Zur Pathologie des Hisschen A-V Bündels bei dem Adams-Stokes'schen Symptomenkomplex (und bei Diphterie), Frankfurt. Ztschr. f. Path. **8**:319, 1911. XV. (*s*) Falconer, A., and Dean, G.: Observations on a Case of Heart Block Associated with Intermittent Attacks of Auricular Fibrillation, Heart **3**:247, 1911-1912. XVI. (*t*) Armstrong, H., and Mönckeberg, J.: Herzblock bedingt durch primären Herztumor bei einem fünfjährigen Kinde, Deutsches Arch. f. klin. Med. **102**:144, 1911. XVII. (*u*) Cohn, A., and Lewis, T.: A Description of a Case of Complete Heart Block, Including the Post-Mortem Examination, Heart **4**:7, 1912. XVIII. (*v*) Cohn, A., and Lewis, T.: Auricular Fibrillation and Complete Heart-Block: A Description of a Case of Adams-Stokes Syndrome Including the Post-Mortem Examination, ibid. p. 15. XIX. (*w*) Griffith, T.: Remarks on Two Cases of Heart-Block, ibid. **3**:141, 1911. (*x*) Kennedy: Supplementary Note on a Case of Heart-Block with an Examination of the Auriculo-Ventricular Junctional Tissue, ibid. **6**:37, 1914. XX. Oppenheimer and Oppenheimer,[sp] case 2. XXI. (*y*) Hoffmann, A.: Die Elektrokardiographie als Untersuchungsmethode des Herzens und ihre Ergebnisse, Wiesbaden, J. F. Bergmann, 1914. Mönckeberg [sn] (1916), p. 90. XXII. (*z*) Gaisböck and Jurak: Klinische und anatomisch-histologische Untersuchungen über einen Fall mit Adams-Stokes'schen Symptomenkomplex, Zentralbl. f. Herz. u. Gefässkr. **7**:37 1915. XXIII. (*a'*) Biedl, A., and Rihl, J.: Ein Fall von Adams-Stokes'schen Krankheit mit Läsionen in beiden Tawara Schenkeln, ibid. **8**:71, 1916. Mönckeberg [sn] (1916), p. 77. XXIV. Mackenzie and Mönckeberg [sn] (1916), p. 105. XXV. (*b'*) Bridgman, E., and Schmeisser: Heart-Block Caused by a Gumma of the Septum, Johns Hopkins Hosp. Rep. **18**:90, 1919. XXVI. (*c'*) Starling, H. J.: Heart-Block Influenced by the Vagus, Heart **8**:31 (Feb.) 1920. (*d'*) Lewis, T.: Post-Mortem Notes of Dr. J. H. Starling's Case of Heart-Block, ibid. **9**:283 (Dec.) 1922. XXVII. (*e'*) Waldo, H., and Herapath, C.: A Case of Complete Heart Block with Post-Mortem Examination, Lancet **1**:271, 1922. XXVIII. (*f'*) Sisto, P.: Studio clinico ed anatomico-pathologico su di un caso di sindrome di Adams-Stokes, Malattie d. cuore **6**:6, 1922. XXIX. (*g'*) Meyer, P., and Oberling, C.: Myocardite tuberculeuse avec syndrome d'Adams-Stokes, Ann. de méd. **14**:368, 1923. XXX. (*h'*) Kauf, E.: Zur Diagnose des Schenkelblocks beim menschlichen Herzen, Ztschr. f. klin. Med. **98**:126, 1924. XXXI (*i'*) Clarke, N., and Smith, F.: Heart-Block of Unusual Etiology, Am. J. M. Sc. **169**:882, 1925. XXXII. (*j'*) Géraudel, E.: Un nouveau cas de syndrome d'Adams-Stokes par lésion transverse du ventriculonecteur, consécutive à une sténose de son artère, Ann. d'anat. path **6**:1075, 1929. XXXIII. (*k'*) Géraudel, E.; Brodin,

2. Gaisböck and Jurak,[8z] 1915. A man, aged 71, had Adams-Stokes attacks for three years. The pulse rate was from 26 to 32 per minute. Brief attacks of paroxysmal tachycardia followed the Adams-Stokes attacks. Polygraphic tracings revealed complete heart block. The heart was enlarged, and there were severe sclerosis of the coronary artery and myocardial fibrosis. The histopathologic examination showed complete interruption of the left branch at its origin by atrophy and fibrocalcareous replacement and complete destruction of the end of the right branch by the same type of lesion.

3. Biedl and Rihl and Mönckeberg,[8a'] 1917. A youth, aged 19, had Adams-Stokes attacks. The electrocardiogram was that of complete heart block with left bundle-branch block at first and later right bundle-branch block.[9] The ventricular rate was 26 per minute. The condition of the heart was thought by Ghon to be an example of endocarditis parietalis fibrosa; the valves were not involved. The left bundle branch was destroyed in its upper part by subendocardial fibrosis. The subendocardial portion of the right bundle branch was greatly damaged but not destroyed by fibrosis, which involved also the subjacent myocardium. Mönckeberg characterized this as a case of bursitis of the conduction system, an example of *"selbständige Pathologie des Atrioventrikular-system"* (an independent pathologic process of the atrioventricular system).

4. Mackenzie and Mönckeberg, 1916 (see footnote 8, case XXIV). An old man was known to have had complete heart block with "left bundle-branch block" for three or four years before his death. The heart showed mild valvular and coronary arterial sclerosis. The histopathologic examination revealed destruction of the intramyocardial portion of the right bundle branch by fibrosis. The left bundle branch was involved by intraseptal fibrosis high in its anterior division and lower in its posterior division. Mönckeberg considered this to be a case of old rheumatic myocarditis.

5. Sisto,[8f'] 1922. A man, aged 80, had Adams-Stokes attacks for two months, and congestive heart failure developed. Polygraphs revealed complete heart block with a ventricular rate of 24 per minute. The heart was large, and there was coronary arterial sclerosis with fibrosis of the myocardium. The histopathologic study showed interruption by fibrosis of the left bundle branch near its origin and similar involvement of the right bundle branch at a distance of 6 mm. from its origin.

6. Mahaim,[1] 1931. Observation IV: A man, aged 59, had Adams-Stokes attacks for eight months. The electrocardiogram revealed complete auriculoventricular dissociation with two different, but in general type similar, alternating

P., and Lereboullet, J.: Étude d'um cas de syndrome d'Adams-Stokes mortel. Nécrose transverse du ventriculonecteur par endartérite sténosante de son artère, Arch. d. mal. du coeur **22**:1, 1929. XXXIV. (*l'*) Géraudel, E., and Valensi, A.: Un cas mortel de syndrome d'Adams-Stokes. Lésion transverse du ventriculonecteur. Endartérite sténosante de son artère, Ann. de méd. **25**:472, 1929. XXXV. Yater[3a] (1929). XXXVI-XL. Mahaim[1] (1931), cases I, II, III, IV and XI. XLI. Grant and Camp[3e] (1932). XLII. Don, Grant and Camp[3f] (1932). XLIII. Yater, Lyon and McNabb[3b] (1933). XLIV. Yater, Barrier and McNabb[3c] (1934). XLV. Yater, Leaman and Cornell[3d] (1934). XLVI. Yater and Cornell[3g] (1935). XLVII-XLVIII. Yater, W. M.; Cornell, V. H., and Claytor, T.: Auriculoventricular Heart-Block Due to Bilateral Bundle-Branch Lesions, Arch. Int. Med., this issue, cases 1 and 2.

9. The old terminology for bundle-branch block is used throughout this paper, since we are not convinced of its incorrectness, although it may have to be modified.

ventricular complexes in the form of a bigeminy, giving the picture of "right bundle-branch block." The ventricular rate was 48 per minute, but the pulse rate was 24 per minute. The heart was large, and there was aortic and mitral endocarditis with fibrosis of the myocardium. The fibers of the auriculoventricular node and of part of the main bundle were found on histopathologic examination to be dispersed by fat.[9a] The left branch was completely destroyed high in its course by an old inflammatory lesion. The right branch was destroyed at a lower point by fibrosis.

7. Mahaim,[1] 1931. Observation XI: A man, aged 51, died as a result of congestive heart failure. The electrocardiogram showed what Mahaim interpreted as complete heart block with ventricular tachycardia and so-called arborization block with right bundle-branch predominance. The heart was the seat of an old mitral endocarditis with old and fresh endocardial lesions and diffuse arteriolar alterations. The histopathologic survey showed incomplete disappearance of the left bundle branch in its superior third as a result of endocarditis and arterial fibrosis. There were repeated necrotic lesions of vascular origin in the inferior two thirds of the right bundle branch with destruction in its terminal portion due to successive vascular lesions.

We have studied 3 cases of auriculoventricular heart block due to bilateral bundle-branch lesions. The first case to be reported was one of complete heart block due to complete interruption by fibrosis of both bundle branches, apparently the result of sclerosis of the large coronary arteries. In the second case the patient was observed through all of the stages from sinus rhythm to complete heart block, with the electrocardiographic picture of "right bundle-branch block" existing before and during the phase of partial auriculoventricular block. There was severe fibrosis of the left bundle branch with moderate fibrosis of the right bundle branch, due apparently to arteriosclerosis of the small coronary arteries. The third patient did not have complete auriculoventricular dissociation permanently, but there were periods when partial heart block existed, periods when complete heart block was present, and other periods when there was sinus rhythm. There were variable ventricular complexes, usually suggestive of "right bundle-branch block." The etiology lay apparently in periadventitial fibrosis of the small coronary arteries associated with mild myocardial fibrosis.

REPORT OF CASE 1[10]

Clinical Record.—A judge, aged 65 at the time of his death, had had considerable dyspnea on exertion for thirteen months. Three months before death he had consulted a physician because of severe laryngitis and was found to have a very slow pulse. About two months before death, while taking an early morning walk, he suddenly lost consciousness for a few moments and fell to the street. He was put to bed and kept there, although he did not experience discomfort. His habits had been sedentary. He was accustomed to smoke four or five cigars daily but did not consume alcohol. He had measles, mumps and pneumonia

9a. We do not consider this significant in the production of the auriculoventricular dissociation.

10. The subject was a patient of Dr. Charles W. Barrier of Fort Worth, Texas.

in childhood. A year before death he was rejected for life insurance because of an irregular pulse. He had complained of dizziness and "blind spells" occasionally for a year. Physical examination disclosed nothing of importance except moderate cardiac hypertrophy, a pulse rate of 30 per minute and a blood pressure of 160 systolic and 60 diastolic. A fluoroscopic examination did not add any information. He was kept under observation for one month before death. Saturation with oxygen, atropinization and large doses of barium chloride and of thyroid extract at different times did not alter the ventricular rate. Electrocardiograms made at

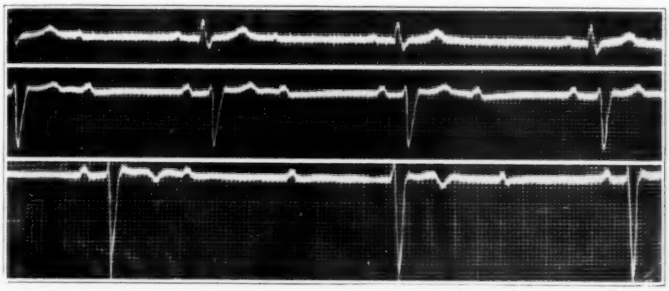

Fig. 1 (case 1).—Electrocardiogram showing complete heart block with slurring of the Q R S complexes, deep S waves in leads 2 and 3 and an inverted T wave in lead 3.

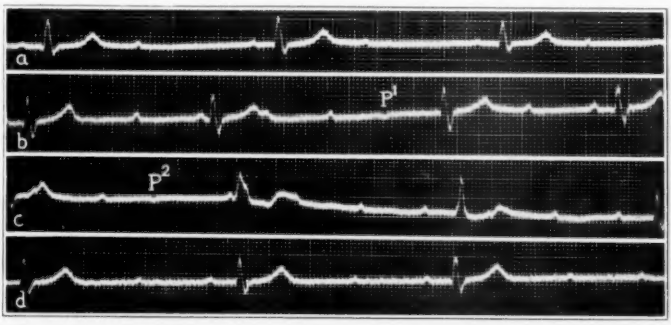

Fig. 2 (case 1).—Lead 1 of four electrocardiograms showing absence of effect on the ventricular rate of (*a*) saturation with oxygen, (*b*) atropinization, (*c*) administration of barium chloride and (*d*) thyroxinization. In *c* there is an aberrant ventricular complex. Minor variations in the ventricular complexes are frequent. The P wave is occasionally premature and inverted (P^1 P^2).

different times all showed complete heart block. The auricular rate varied from 60 to 100; the ventricular complexes were mainly of the so-called supraventricular form with some slurring of the QRS complexes, deep S waves in leads 2 and 3 and an inverted T wave in lead 3 (fig. 1). In one of the electrocardiograms an abnormal ventricular complex replaced one of the complexes of usual form, and minor variations were present even in these (fig. 2).

While under observation the patient was subject to attacks of weakness and faintness during which the pulse rate dropped to 20 per minute. Eleven days before death he had an attack of unconsciousness while lying in bed; the pulse rate was 24 per minute. On the tenth day before death Cheyne-Stokes respiration occurred intermittently, the pulse rate remaining 20 per minute. Eight days before death digitalization was begun, and during the remaining period of life dyspnea occurred about every other night, for which morphine was used. In general, the patient felt well. On the day of death (July 23, 1931) he had marked dyspnea and was cold and clammy. The pulse rate was 26 per minute. This attack was recovered from, but later death occurred in an Adams-Stokes attack.

Necropsy.—There was marked cyanosis of the body. The external jugular veins were greatly distended. There was about 200 cc. of clear straw-colored fluid in each thoracic cavity, but the lungs were essentially normal. All of the other organs except the heart were also essentially normal.

Gross Description of the Heart.—The heart weighed about 450 Gm. The myocardium appeared to be normal. The anterior descending coronary artery was sclerotic, and about 3 cm. from its origin it was constricted to about one quarter of its normal caliber. The other coronary arteries were somewhat thickened, but their lumens were of normal diameter. The endocardium and valves appeared normal.

Histopathologic Examination of the Heart.—Nine blocks of tissue were removed from the auriculoventricular and the interventricular septums. Blocks 1 and 2 included the entire thickness of the septum and contained the auriculoventricular node and bundle and the origins of the two bundle branches. These two blocks were sectioned vertically from behind forward. Blocks 3, 4 and 5 included the marginal trabeculum of the right ventricle and half of the thickness of the interventricular septum. They contained all of the microscopically recognizable right bundle branch below its origin and were sectioned horizontally from above down. Blocks 6, 7, 8 and 9 included almost the entire left side of the interventricular septum (muscular portion) with half of its thickness. Blocks 6 and 7 lay above blocks 8 and 9. These blocks contained all of the microscopically recognizable left bundle branch and were sectioned horizontally from above down. Serial sections, 10 microns thick, were made of all the blocks, and every twentieth section was mounted and stained with Van Gieson's connective tissue preparation. All intervening sections were saved, unmounted and unstained. In all, about 10,000 sections were cut.

The auriculoventricular node and bundle were normal. The artery supplying the node was relatively small and showed very moderate subintimal fibrosis. In the very origin of the left bundle branch there was a small rounded fibrous plaque which did not seem to interfere seriously with the continuity of the branch. Such a plaque should not be considered abnormal for the heart of an older person. Shortly below its origin, however, the left bundle branch began to show dense fibrosis, but the subjacent myocardium was relatively normal. The entire width and thickness of the left branch were so affected that few of the conduction fibers were visible in the dense fibrous tissue. This fibrosis was seen in all of the sections containing the left bundle branch, but in the lower half of the septum the fibrosis was not so severe as in the upper half (fig. 3). Shortly below its origin the right bundle branch also began to become fibrotic. The fibrosis rapidly became more severe until in the upper third of the branch, which is mainly intramyocardial, there was a small section in which no muscular elements

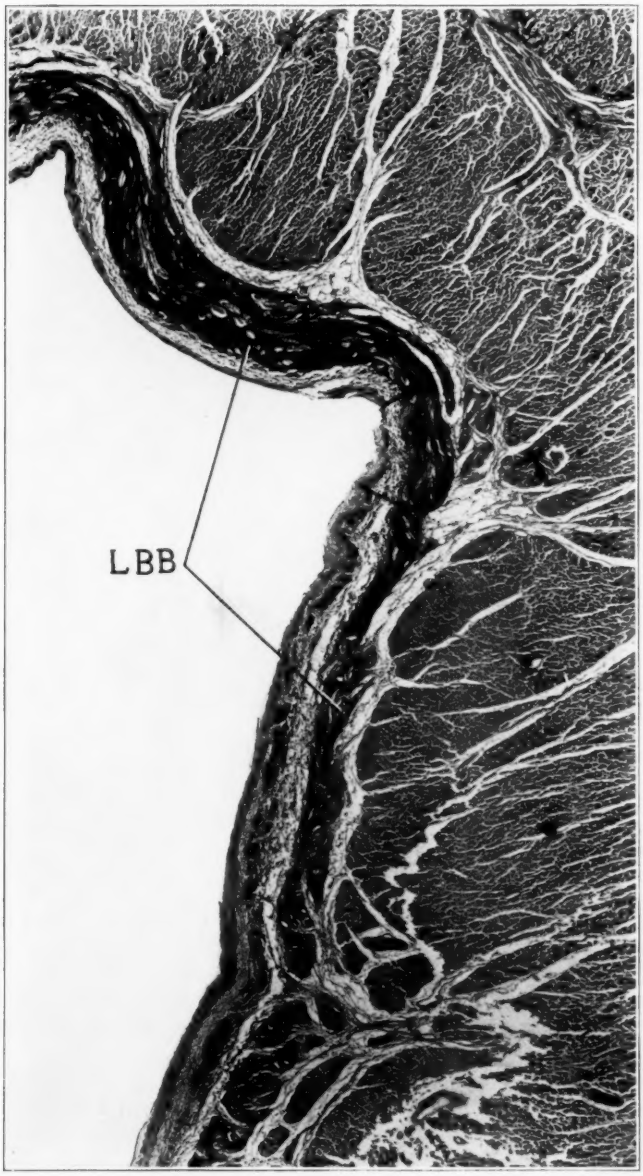

Fig. 3. (case 1).—Section 60, block 7, showing fibrous replacement of the left bundle branch, *L B B*, in horizontal cross-section, with normal subjacent myocardium; × 40.

of the branch were visible (fig. 4). This fibrosis slowly diminished, and for some distance before the branch became subendocardial it appeared entirely normal again and continued so for the remainder of its recognizable course. The myo-

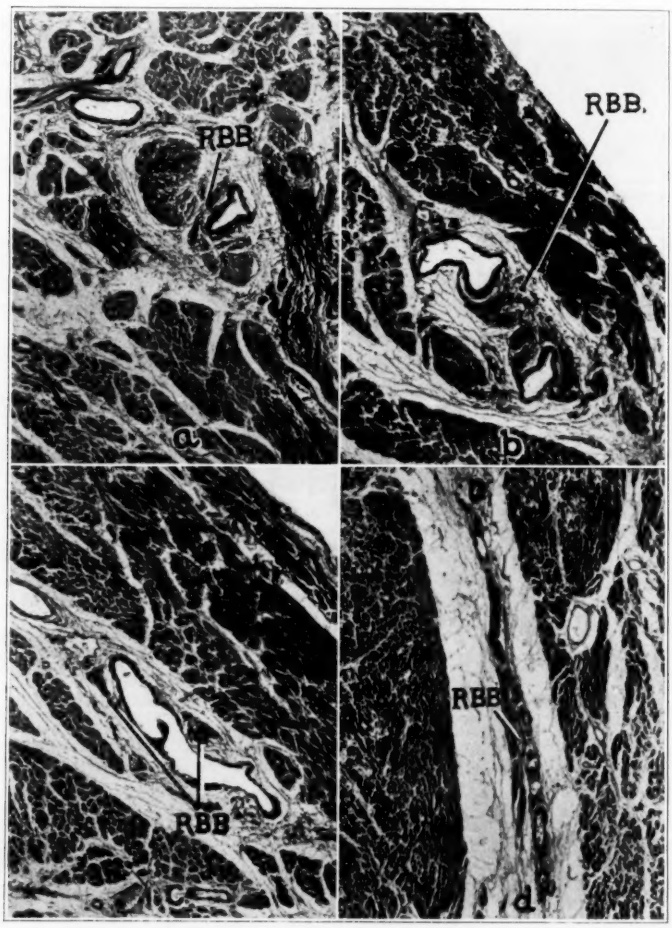

Fig. 4 (case 1).—(*a*) Section 660, block 2, showing moderate fibrosis of the right bundle branch, *R B B*, in oblique cross-section; × 40. (*b*) Section 810, block 2, showing fibrosis of the right bundle branch, *R B B*, in horizontal cross-section; × 40. (*c*) Section 1020, block 2, showing complete replacement of the right bundle branch, *R B B*, by fibrous tissue, in horizontal cross-section. A large vein is seen accompanying the branch at this point; × 40. (*d*) Section 440, block 3, showing beginning diminution of the fibrosis of the right bundle branch, *R B B*, lower in its intramyocardial portion, in horizontal cross-section; × 40.

cardium surrounding the right bundle branch appeared to be normal, but some of the smaller arteries in the septum were slightly sclerotic.

Summary of Case 1.—A man, aged 65, had had dyspnea on exertion and spells of dizziness, faintness and unconsciousness for more than a year before death. Complete heart block was known to have existed for three months before death, which occurred in an Adams-Stokes attack. The heart was moderately enlarged, and the coronary arteries were sclerotic, but the myocardium appeared grossly to be normal. Serial sections through the conduction system showed dense fibrosis with practically complete destruction of the whole upper half of the left bundle branch and moderate fibrosis of the lower half. The right bundle branch was also completely destroyed by fibrosis in its upper third and partly replaced by fibrous tissue in its middle third, but its lower third was normal. The myocardium was microscopically essentially normal throughout.

REPORT OF CASE 2

Clinical Record.—A business man, aged 63 at the time of death in 1933, had been a patient of one of us (T. A. C.) since March 1923. His usual complaint was of some minor digestive trouble. He had a severe attack of typhoid fever in his youth and had been treated for a possible peptic ulcer some years before. He had had gonorrhea which had resulted in chronic prostatitis. He used alcohol and tobacco moderately. He led an active life and played golf frequently. He was of a very nervous temperament. Repeated physical examinations had given negative results except for a slightly low blood pressure. While playing golf in June 1929 he fell unconscious but recovered quickly, regaining his feet before his companions could reach him. Physical examination that afternoon was reported to have yielded negative results. A few days after this episode he had a spell of "light-headedness" but did not faint. During August he played golf every day without inconvenience other than that of great fatigue. Early in October he began to have dizzy spells again. A physical examination in December gave essentially negative results. The blood pressure was 110 systolic and 60 diastolic. An electrocardiogram taken Dec. 3, 1929 was normal, but the amplitude of the QRS complex was 0.12 second (normally from 0.6 to 0.1 second) and the PR interval was 0.20 second, the upper limit of normal.

Until July 1930 he was free from bad attacks of giddiness but complained of abdominal "gas" and fatigability. A Graham-Cole study of the gallbladder performed in the course of a thorough investigation showed it to be probably pathologic, but operation was not performed. In the latter part of July 1930 he lost consciousness momentarily, and at this time his wife noted that his pulse rate was 52 and the rhythm regular. A short time later his pulse rate was 60, and the next day it was normal. The cardiac examination gave normal results. On August 1, while shaving on a train, he became faint and dizzy and remained so during the day. That night he fainted, and his pulse rate was noted to be 28. For the next five weeks he felt very ill (weak and dizzy), and the pulse rate ranged from 24 to 38. On September 4 the pulse rate reached 50 for the first time. The physician treating him at that time (he was away from home) gave him a hypodermic injection of 12 minims (0.74 cc.) of 1:1,000 solution of epinephrine hydrochloride. Most alarming symptoms followed. There was violent trembling, his head felt as if it would burst, the dizziness became severe, his pulse rate rose rapidly to 80 and then dropped to 20, there was gasping for breath, and he felt that he was dying. On September 20 an electrocardiogram showed typical "right bundle-branch block" (old terminology) except that the T wave

was in the same direction as the QRS complex in lead 3. The heart sounds at this time were faint and distant, and a soft systolic murmur was audible over the precordium, but the heart was apparently not enlarged. An electrocardiogram taken on November 3 was similar to that made in September, but a short period of partial auriculoventricular block was disclosed, with an aberrant ventricular complex of extrasystolic form preceding each usual complex during the period of block (fig. 5). For the next few months the pulse rate was very irregular, ranging from 32 to 70. The administration of atropine and barium chloride gave no relief but seemed to cause the formation of more "gas." Dyspnea on exertion was noted. An electrocardiogram made on December 10 was essentially the same as the one made in November, with minor differences in the QRS complexes, but one made on Jan. 7, 1931 showed a definitely established 2 to 1 auriculoventricular block. At this time, however, the ventricular complexes were

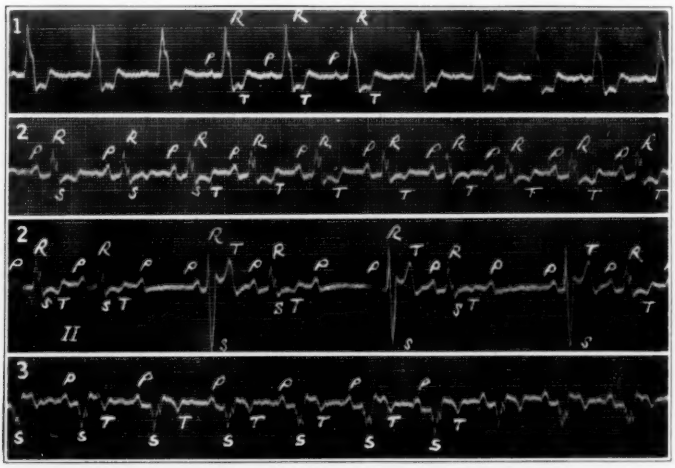

Fig. 5 (case 2).—Electrocardiogram showing "right bundle-branch block" (old classification), typical except for inversion of the T wave in lead 3. The duration of P R was 0.24 second; of Q R S, 0.12 second. In the second strip of lead 2 there is a period of 2 to 1 heart block during which there is an aberrant ventricular complex of extrasystolic form preceding each usual complex.

essentially normal, without notching but with some spreading of the QRS complexes (0.1 second in lead 1; 0.12 second in leads 2 and 3), and the T waves were upright. An electrocardiogram made on April 18 was similar except for inversion of the T wave in leads 2 and 3 and a moderately high S T segment in these leads. After the development of the constant 2 to 1 block the course was fairly satisfactory until July 12, when, at the country club, he had a severe spell of repeated attacks of dizziness and faintness lasting for four hours. The face paled, the pulse ceased for varying lengths of time, and the muscles twitched slightly. Ephedrine (¾ grain [0.02 Gm.]) seemed to afford some relief. After the attack he was again fairly comfortable, was able to be driven about in an automobile, walked short distances, and transacted some business over the tele-

phone. An electrocardiogram made on Dec. 16, 1932, was very similar to that of April 18, 1931, but the T waves in leads *2* and *3* were more deeply inverted, and the S T segment was iso-electric (fig. 6).

On Jan. 1, 1933, after being on his feet rather too long at a social gathering, he had another setback and had to go to bed for about two weeks. On January 21 he became very ill with almost continuous convulsive seizures for forty-eight hours, the pulse at times being as low as 10 per minute and the respirations down to 8. This condition was considerably relieved by the oxygen tent, which was used for about one week. During the period of continuous convulsions there was evidence of edema of the lungs with basal râles and bloody expectoration. An electrocardiogram made on January 27 showed that an independent ventricular rhythm had been established, with low voltage, notched QRS complex of 0.12 second, prolonged S T interval and inverted T wave in leads *2* and *3*. For some weeks he did not have syncopal attacks, but from this time on he was delirious

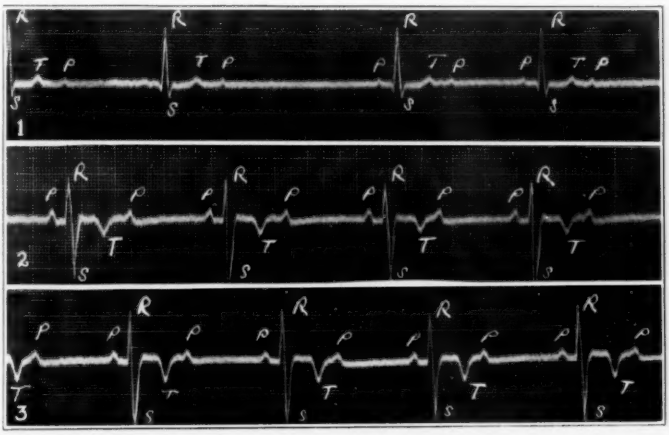

Fig. 6 (case 2).—Electrocardiogram showing established *2* to 1 heart block. P R equals 0.24 second; Q R S, 0.14 second. In lead 1 there is transient sino-auricular block. There is inversion of the T wave in leads *2* and *3*.

the greater part of the time. The most distressing symptom was Cheyne-Stokes breathing, from which he had no relief except while under the effects of morphine. The last electrocardiogram, made on April 6, showed persistence of complete block, but the voltage was no longer as low as before, and the picture again suggested "right bundle-branch block" (fig. 7). The blood pressure, which had always been relatively low, became variable during the last illness, ranging as high as 220 systolic, with a relatively low diastolic pressure of from 65 to 80. All of the drugs which have been found to give relief in other cases of heart block, such as barium chloride, atropine, epinephrine, ephedrine, etc., were tried at various times, but none except ephedrine seemed to have any good effect and that only to a small degree. On April 11 the convulsions and periods of unconsciousness started again. The pulse stopped at times for five minutes, according to the nurse. The condition became desperate. The temperature rose to 104 F., and death occurred on April 13, almost four years after his first attack on the golf links.

Gross Description of the Heart.—Examination of the heart only was permitted. It weighed 450 Gm. The epicardial fat was normal in amount. The epicardium appeared normal except for some roughening on the anterior surface of the right ventricle in an area about 1 cm. in diameter. After being opened in the usual manner the chambers were seen to be normal in size and not dilated. The endocardium and valves appeared to be entirely normal. The myocardium showed no evidence of fibrosis on tangential section. The root of the aorta was smooth. The coronary arteries were not atheromatous or thickened, and their lumens were normal. The left coronary artery supplied more of the myocardium than usual; its circumflex branch extended around to the posterior interventricular sulcus and gave off the posterior as well as the anterior descending branch. The right coronary artery was about half normal in size and consisted only of a circumflex branch and some marginal branches. The endocardium of the interventricular septum on the left side was yellowish but did not appear different from that of most hearts in this respect.

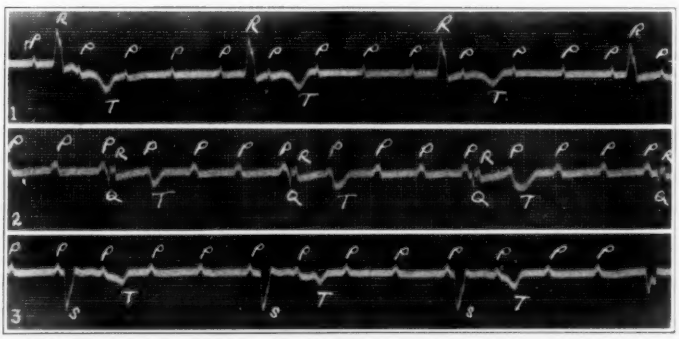

Fig. 7 (case 2).—Electrocardiogram showing established complete heart block, the auricular rate being 110 per minute, the ventricular 30. Q R S equals 0.12 second. There is inversion of the T wave in all leads. The S T interval is greatly prolonged. Left ventricular preponderance is shown.

Histopathologic Examination of the Heart.—Four main blocks were removed which included the greater part of the auriculoventricular and the interventricular septums. The largest of these blocks contained the auriculoventricular node and bundle and the origin of the bundle branches. To facilitate fixation this block was divided vertically into nine blocks of equal size (numbered from 1 to 9 inclusive). These blocks were sectioned vertically from behind forward so that the conduction system could be followed progressively from its origin. The other three blocks included the muscular part of the interventricular septum and were designated A, B and C from above down. These contained the bundle branches as far down as they could be followed. These blocks were sectioned horizontally from above down. Another block was removed posterior to the large first block and contained all of the artery to the auriculoventricular node up to the part included in the large block. This block was sectioned vertically from behind forward. All of the blocks were embedded in paraffin, and serial sections of 10 microns of thickness made. Every fifth section of most of the nine small blocks was mounted and

stained. Every fifth section of block A and every twentieth section of the other blocks were mounted and stained. Van Gieson's connective tissue stain was employed. In all, about 4,000 sections were cut. All sections not mounted and stained were preserved.

The artery supplying the auriculoventricular node was very large. Its lumen was good throughout. Its wall was moderately thickened owing to subintimal fibrosis. A large collar of fat accompanied this artery from the auriculoventricular

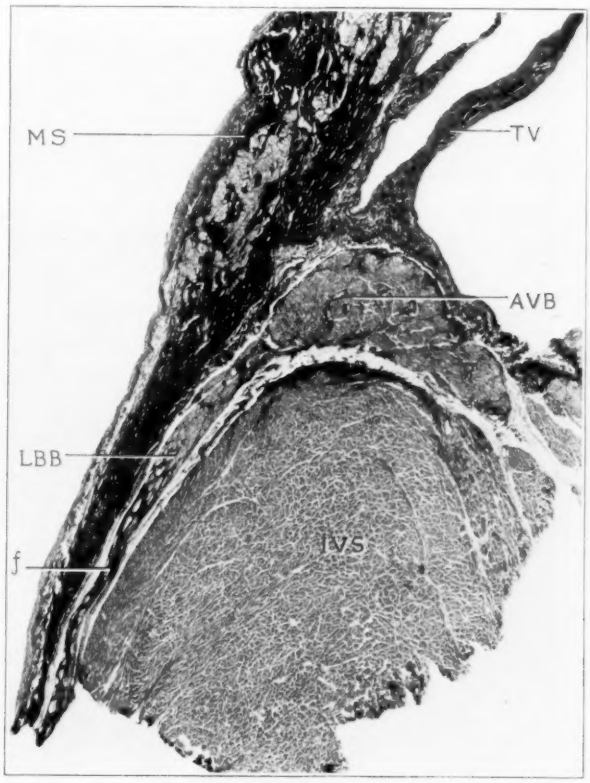

Fig. 8 (case 2).—Section 25, block 7, showing the essentially normal bundle of His, *A V B*, in vertical cross-section, and the upper portion of the left bundle branch, *L B B*, with severe fibrosis *f*. *M S* indicates the membranous portion of the interventricular septum; *T V*, the tricuspid valve, and *I V S*, the muscular portion of the interventricular septum; × 40.

sulcus into the auriculoventricular septum, and this fat more or less surrounded the subendocardial border of the node. The fibers of the node were still united to the auricular myocardium at scattered points through the fat tissue. This is a common finding in the hearts of patients of middle life or old age. The auriculo-

ventricular node and bundle were histologically normal except for a moderate increase in fibrous connective tissue in the distal portion of the bundle. This connective tissue formed more or less definite fibrous trabeculae between the muscle fasciculi, but there was no destruction of the muscle. Just below its origin the left bundle branch was seen to contain dense fibrous tissue (fig. 8). This fibrous tissue extended throughout the entire breadth of the left bundle branch and was confined to it, the subjacent myocardium being free from an abnormal amount of fibrous

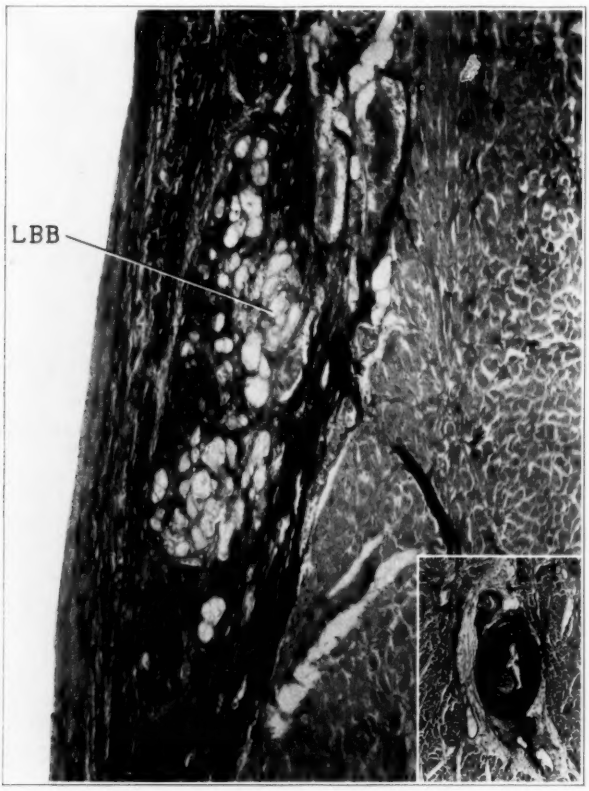

Fig. 9 (case 2).—Section 190, block 7, showing marked fibrosis of a portion of the left bundle branch, *L B B*, in vertical cross-section, with the subjacent myocardium relatively normal; × 135. The inset shows a sclerotic small artery of the interventricular septum; × 40.

tissue. As the branch was followed down the septum it was found to be practically completely replaced by fibrous tissue in its upper half, except for an occasional small group of Purkinje fibers buried in this tissue (fig. 9). In the lower half of the septum the fibrosis of the left branch slowly cleared up so that, except for a small border of fibrous tissue, the branch appeared normal. The

very first portion of the right bundle branch contained somewhat more than the normal amount of connective tissue. As the branch descended and became intramuscular the fibrous tissue increased in amount until about one third of the branch consisted of fibrous tissue (fig. 10). This fibrosis was confined to the branch; i. e., it did not involve the adjacent myocardium. As the branch was followed lower the amount of fibrous tissue diminished, and at about the junction of its upper and middle thirds the branch became normal and continued so. Both branches were followed onto the papillary muscles until the Purkinje elements could no longer be recognized with certainty.

The myocardium throughout seemed to be normal, but the small arteries in the interventricular septum were thickened here and there, markedly in places, and the lumen was greatly reduced at these points (fig. 9, inset). These arterial changes were most notable about the middle of the septum and were most pronounced nearer the left side.

Summary of Case 2.—A man, aged 63, had had Adams-Stokes attacks for nearly four years. Electrocardiograms taken at intervals during this period showed numerous changes in the ventricular complexes. Before 2 to 1 heart block was established the form was almost typically that of "right bundle-branch block." After 2 to 1 heart block had become established the electrocardiographic picture of bundle-branch block no longer existed. Finally, complete heart block supervened, with the reappearance of "right bundle-branch block." Death occurred during a prolonged convulsive seizure. The heart was slightly enlarged and appeared grossly normal. The larger coronary arteries were not altered. Serial sections through the conduction system showed fibrosis confined mainly to the bundle branches. The upper half of the entire left bundle branch was almost completely replaced by dense fibrous tissue; the lower half was almost normal. The upper third of the right bundle branch was moderately fibrotic, about one third of its cross-section being replaced by fibrous tissue. The lower two thirds of the branch was essentially normal. The myocardium appeared to be normal, but the small arteries in the interventricular septum were considerably thickened and narrowed in places.

REPORT OF CASE 3

Clinical Record.—The patient, a retired army major, aged 49 at the time of death, had been retired at the age of 35 because of bilateral choroidoretinitis of undetermined cause. He remained well, however, until fourteen months before death, suffering only from poor vision. He then began to have dyspnea on exertion and a smothering sensation when he walked about 10 blocks. He had had the ordinary diseases of childhood, malaria at 19, mumps at 26 and gonorrhea without complications at 29. About two months after the dyspnea began he became dizzy after playing eight holes of golf, rested a couple of minutes and proceeded to play until he reached the eighteenth hole, where he had a second dizzy spell of brief duration. The next night he noticed that his pulse was irregular and slow, the rate being about 40 per minute. He entered Walter Reed General Hospital for examination and treatment, and in the ensuing year was a patient there during five different periods. During this time electrocardiograms were made at varying intervals. These will be considered together later. On the first admission the ocular condition was found to be an inactive choroidoretinitis, and there was moderate retinal arteriosclerosis. Degenerative heart disease was diagnosed on the basis of the electrocardiogram. There was no evidence of chronic passive congestion. On the second admission to the hospital in May 1933, besides the ocular and cardiac conditions, generalized arteriosclerosis and subacute thrombotic occlu-

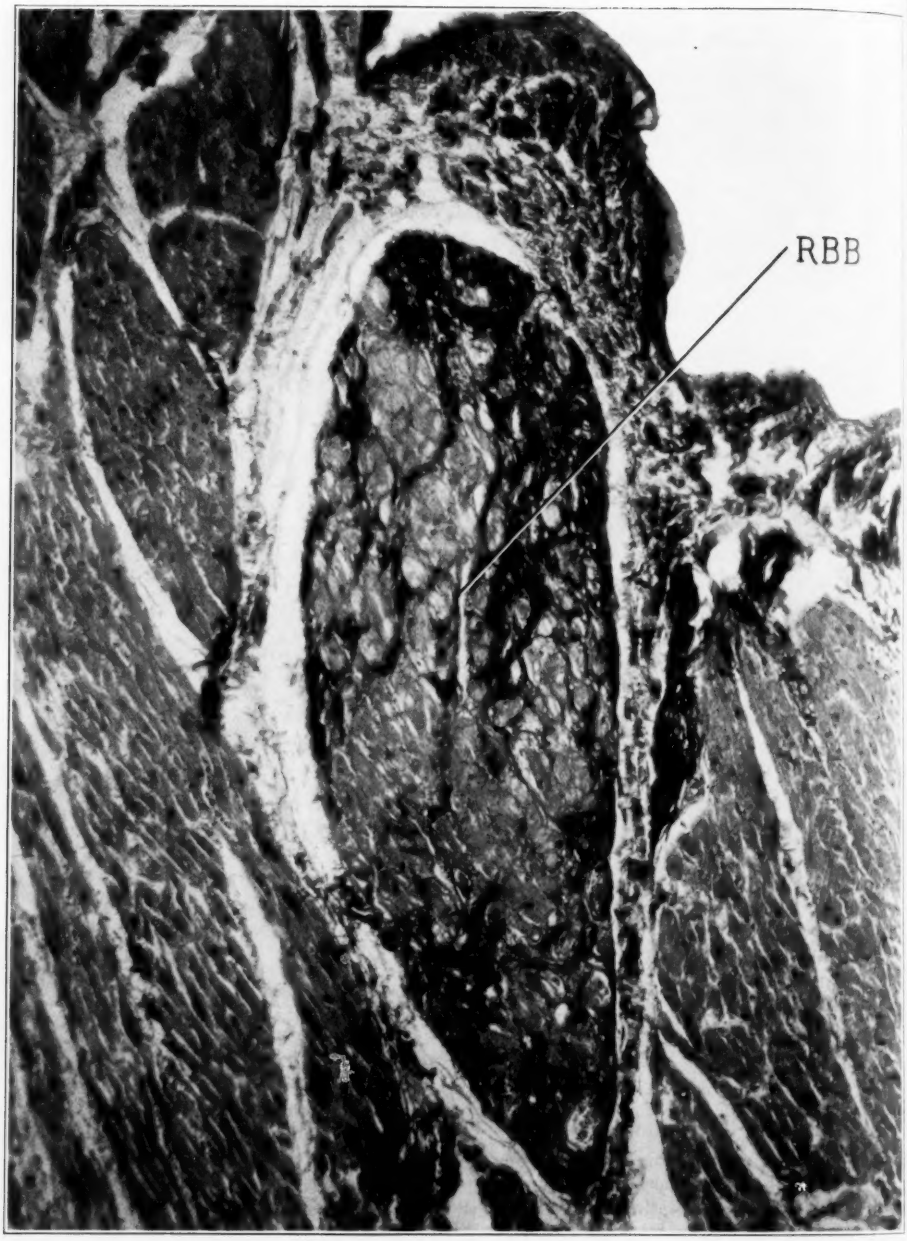

Fig. 10 (case 2).—Section 190, block 7, showing the moderately fibrotic right bundle branch, *R B B*, in oblique cross-section, with the surrounding myocardium relatively normal; × 135.

sion of the right posterior tibial artery were diagnosed. The latter progressed, with severe pain, and on the last admission there was early gangrene. Physical examination at this time revealed a fairly well nourished man, prematurely aged. There was great visual impairment. The heart was not enlarged. There was a variable faint systolic murmur, most intense at the mitral area. The ventricular rate was 38 to 42 per minute. The blood pressure in the arms was 132 systolic and 88 diastolic. The lungs were normal. The abdomen was normal. The remainder of the examination revealed nothing of importance except in the right leg and foot, where there was evidence of complete occlusion of the arterial tree from above the popliteal artery, beginning gangrene of the little toe and possible superficial phlebitis of the leg midway between the knee and ankle.

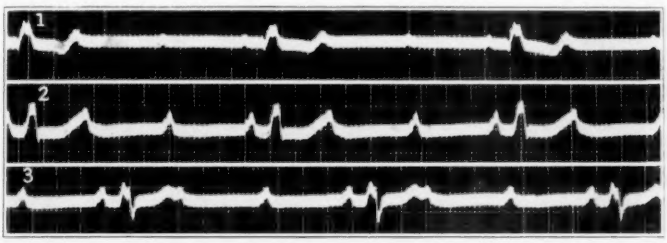

Fig. 11 (case 3).—Electrocardiogram made May 23, 1933, showing 3 to 1 heart block and "incomplete right bundle-branch block" (type 1, see text).

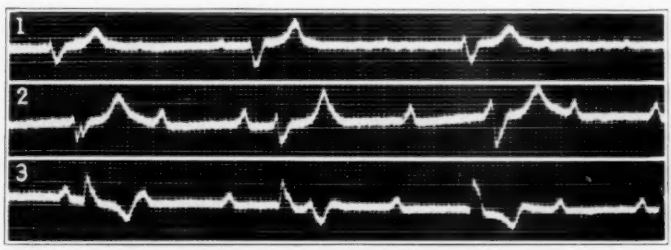

Fig. 12 (case 3).—Electrocardiogram made May 16, 1933, showing complete heart block and "left bundle-branch block" (old classification). The Q R S complexes vary. Q R S equals from 0.14 to 0.16 second (type 2, see text).

Urinalyses, a hemogram, Wassermann and Kahn reactions of the blood and the urea nitrogen of the blood were all normal. Treatment of the vascular condition was begun, and amputation was finally undertaken. Soon after administration of the nitrous oxide and oxygen anesthetic was begun, however, the patient died.

The electrocardiograms made during the year of observation show two main separate and distinct types of ventricular complexes, which changed from time to time from one type to the other. One type was present at the times when there was sinus rhythm or incomplete auriculoventricular block (type 1); the other, when there was complete auriculoventricular block (type 2). Minor changes in the ventricular complexes occurred frequently in both types. The

voltage was moderately low in both. The ventricular complexes of both types were most constant in lead 1. In type 1 (fig. 11) the main ventricular complex of lead 1 consisted of the R wave, which was greatly slurred and unaccompanied by Q or S waves, its duration ranging from 0.13 to 0.15 second, its amplitude being never over 6 mm.; the T wave was either diphasic or upright, usually the latter. In lead 2 of type 1 the main ventricular deflection was also a very similar R wave with or without a small S wave, the latter varying in size at different times; the T wave was either diphasic or upright, usually the latter. In lead 3 of type 1 the S wave was usually the most prominent part of the ventricular complex, but there was always a small R wave which was notched on its downward slope. The greatest amplitude of the S waves was about 6 mm. The T

Fig. 13 (case 3).—Electrocardiogram made May 22, 1933, showing complete heart block, and "bundle-branch block" intermediate between "right and left bundle-branch block." Q R S equals 0.13 to 0.15 second (type 2, see text).

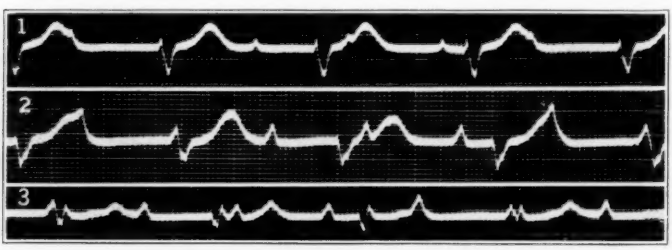

Fig. 14 (case 3).—Electrocardiogram made Oct. 3, 1933, showing complete heart block and "incomplete left bundle-branch block" (type 2, see text).

wave in lead 3 was always upright. Type 1 might therefore be called "incomplete right bundle-branch block" according to present conceptions or perhaps so-called arborization block of the "right bundle-branch block" form. Type 2 (figs. 12, 13 and 14) was more variable than type 1, mainly in leads 2 and 3, but in a general way it presented a picture the opposite of that of type 1, viz., "incomplete left bundle-branch block" or "arborization block" of the "left bundle-branch block" form. The main ventricular deflection in lead 1 was always the S wave, usually accompanied by a small R wave; the S wave was always slurred but of low amplitude and of a duration of from 0.13 to 0.15 second; the T wave was always upright and moderately large. In lead 2 of type 2 the main ventricular deflection was the S wave on three occasions and the R wave on one occasion (as in type 1);

it was always badly slurred or even notched; the T wave was always upright, and when accompanying the S wave it was considerably enlarged. In the first electrocardiogram of type 2 the main ventricular deflection of lead 3 was a badly slurred R wave without Q or S waves, and the T wave was inverted (fig. 12). In the second electrocardiogram of type 2 the R and S waves were of the same small amplitude with slurring of the downstroke of the R wave (as in type 1), and the T wave was upright (fig. 13). In the third electrocardiogram of type 2 the main ventricular deflection was the S wave unaccompanied by an R wave, and the T wave was upright; in this electrocardiogram the main deflection of all three leads was the S wave, accompanied by upright T waves. In the fourth electrocardiogram of type 2 there were small Q, R and S waves and the T wave was directed upward (fig. 14). The following is a brief summary of all of the 1933 electrocardiograms:

1. January 23: Sinus rhythm with short runs of 2 to 1 auriculoventricular block; "incomplete right bundle-branch block" (type 1).

2. January 26: 2 to 1 auriculoventricular block; "incomplete right bundle-branch block" (type 1).

3. February 3: Practically identical with no. 2.

4. February 13: Practically identical with nos. 2 and 3.

5. May 15: Complete auriculoventricular heart block; "complete left bundle-branch block" except for low amplitude (type 2, fig. 12).

6. May 22: Complete auriculoventricular block; mixed "bundle-branch block," lead 1 being of type 2, leads 2 and 3 of type 1 (fig. 13).

7. May 23: A 3 to 1 auriculoventricular block; "incomplete right bundle-branch block" (type 1, fig. 11).

8. July 11: Complete auriculoventricular block; mixed "bundle-branch block," the main ventricular complex being the S wave in all three leads, the T wave being upright in all leads (type 2).

9. October 3: Complete auriculoventricular block; "incomplete left bundle-branch block" (type 2, fig. 14). This electrocardiogram is intermediate in form between nos. 5 and 6.

10. October 9: A 2 to 1 auriculoventricular block; "incomplete right bundle-branch block" (type 1); similar to nos. 2, 3 and 4.

11. November 23: Practically identical with nos. 2, 3, 4 and 10.

12. November 24: Practically identical with nos. 2, 3, 4, 10 and 11.

13. December 8: Two similar electrocardiograms with sinus rhythm and "complete right bundle-branch block" except for the low voltage and diphasic T wave in lead 1 (type 1), very similar to no. 1.

14. December 30: Two similar electrocardiograms with 3 to 1 auriculoventricular block and "incomplete right bundle-branch block" (type 1), similar to no. 7.

The ventricular rate varied during the year from 37 to 72 per minute according to the presence of sinus rhythm or partial or complete auriculoventricular block. The auricular rate varied from 72 to 94 per minute.

Necropsy (performed by Major Hugh Mahon, M.C., U. S. Army, pathologist, Walter Reed General Hospital).—Besides the cardiac lesions, which will be described in detail, the main anatomic diagnoses were: slight generalized arteriosclerosis, especially of the smaller vessels; mural thrombosis in the terminal portion of the arteriosclerotic abdominal aorta; arteriosclerosis and organized

thrombosis of the vessels of the right leg from the anterior iliac artery to the dorsalis pedis artery; congestion of the internal viscera; pulmonary edema with atelectasis of several lobes; scar, probably arteriosclerotic, in the lower pole of the right kidney, and linear scar of the spleen.

Gross Description of the Heart.—The heart weighed 410 Gm. The myocardium was flabby and grayish red. In the posterior wall of the left ventricle near the apex and close to the septum there was a small scar, 0.8 cm. in diameter, with fine yellowish mottling. In the interventricular septum near the base anteriorly there was also a suggestion of scarring. The coronary arteries appeared normal, with an occasional small, slightly elevated atheromatous plaque. The endocardium and valves were apparently normal. The ascending portion of the aorta was slightly atheromatous.

Histopathologic Examination of the Heart.—Besides sections from small blocks of tissue from various parts of the myocardium, serial sections were made from blocks which included the whole of the auriculoventricular and interventricular septums. Owing to the fact that numerous incisions had been made into the muscular portion of the interventricular septum eight blocks of tissue of various sizes were excised and carefully recorded in diagrams. Block 1 was the largest and included the auriculoventricular node and bundle and about 1 cm. of the first portion of both bundle branches. Serial sections 10 microns thick were cut vertically from behind forward. The serial sections of the remaining blocks were made horizontally from above down. Every twentieth section of each block was mounted and stained with Van Gieson's connective tissue preparation. Later, every fifth section of block 1 was mounted and so stained. In all, about 8,500 sections were cut.

The auriculoventricular node and bundle appeared to be normal. There was questionable increase in the connective tissue of the terminal portion of the bundle. From its very origin the left bundle branch in its entire thickness and breadth was extremely fibrotic, approximately 60 per cent of the conduction tissue having been destroyed and replaced by fibrous tissue (fig. 15). In some places the conduction tissue was totally replaced by fibrous tissue; in others it was embedded in or surrounded by fibrous tissue. This fibrosis was greatest in the first centimeter of the branch. Below that, it rapidly diminished in amount, more rapidly in the posterior division of the branch, until at about the lower edge of the upper third the branch was almost normal. The fibrosis was apparently not the result of endocardial disease but of intrinsic damage. The right branch was also fibrotic from its very origin, but the fibrosis did not reach a maximum degree until about the middle of the intramyocardial portion, i. e., about the middle of the course, where the branch was replaced by fibrous tissue to the extent of about 75 per cent. There were relatively few conduction fibers, and these were embedded in dense fibrous tissue (fig. 16). Below this region the degree of fibrosis rapidly diminished until the branch, still intramyocardial, soon became quite normal and continued so for the remainder of its course. The fibrosis of the branches was confined to them, the surrounding and subjacent myocardium being almost normal. There was slight to moderate generalized increase in connective tissue in the myocardium of the septum, and the fibrous trabeculae carrying the larger arteries in the myocardium were moderately increased in thickness and density. The arteries themselves, however, did not appear to be more than slightly sclerosed. In two of the blocks the anterior descending branch of the left coronary artery was included. This showed some subintimal fibrosis, but the lumen was not diminished in caliber. In the area near the apex of the left

ventricle already mentioned as being scarred there was extensive dense fibrosis without cellular infiltration. Included in the scar were some small islands of fat cells. In sections from other parts of the myocardium the appearance was the same as that of the septum.

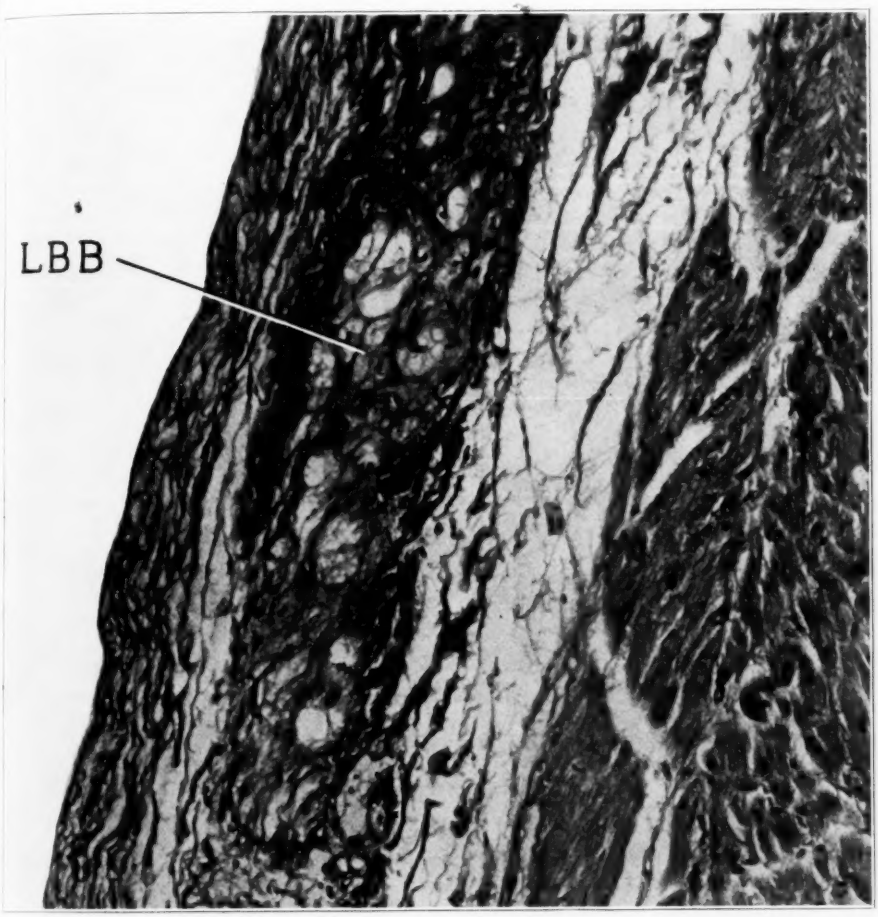

Fig. 15 (case 3).—Section 1480, block 1, showing fibrosis of a portion of the left bundle branch, *L B B*, in vertical cross-section, with the underlying myocardium relatively normal; × 235.

Summary of Case 3.—A man, aged 49, had some dyspnea on exertion and occasional dizzy spells for over a year before death. Thrombotic occlusion of the arteries of his right leg developed, and he died under the anesthetic before amputation could be performed. Numerous electrocardiograms made during the

last year of life showed varying degrees of auriculoventricular heart block with some periods of sinus rhythm. In all of the electrocardiograms there was evidence of impaired conduction of one or the other bundle branch, more often of the

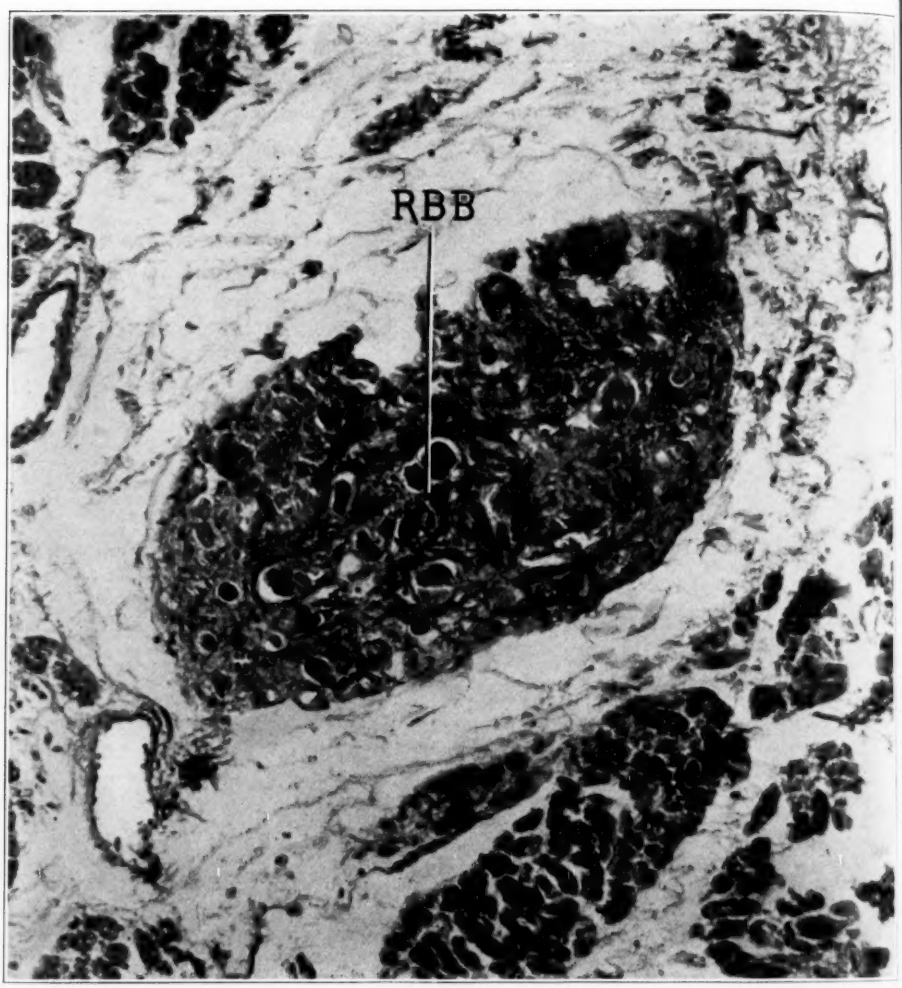

Fig. 16 (case 3).—Section 1100, block 3, showing the very fibrotic portion of the right bundle branch, *R B B*, in horizontal cross-section; × 235.

right. The heart was slightly enlarged and was grossly almost normal. Serial sections through the conduction system showed fibrosis confined to the bundle branches, about 60 per cent of the track of the left branch being replaced and about

75 per cent of the cross-section of the right branch. This fibrosis was most marked in the upper third of the left branch, the entire width being involved, and in the middle third of the right branch. There was slight increase of connective tissue in the myocardium with moderate increase in the fibrous tissue of the trabeculae carrying the intramyocardial arteries. The large coronary arteries were only slightly affected. There was a small scar near the apex of the left ventricle.

ELECTROCARDIOGRAPHIC ALTERATIONS IN SO-CALLED UNILATERAL BUNDLE-BRANCH BLOCK

Rothberger and Winterberg [11] and later Lewis [12] described the electrocardiographic effects of section of the bundle branches separately in experimental animals (chiefly, the dog). These effects have been repeatedly verified, mainly by Wilson and Herrmann [13] and by Smith.[14] The results were as follows: In lesions of the left bundle branch the chief ventricular deflections of leads 2 and 3 were exaggerated R and T waves, the former directed upward, the latter downward; in lead 1 the deflections were generally of lesser amplitude but similar in direction. In lesions of the right bundle branch the chief deflections of leads 2 and 3 were exaggerated S and T waves, the former directed downward, the latter upward; in lead 1 the first deflection was sometimes upward (R wave), and it was then followed by a downward directed T wave, but more often the deflections were small and directed as in leads 2 and 3.

The electrocardiograms of human beings similar to these descriptions have been thought to represent failure of one or the other bundle branch to conduct (Lewis [15]) and the condition has been designated bundle-branch block. Pure "left bundle-branch block" is supposed to correspond to the dextrocardiogram and pure "right bundle-branch block" to the levocardiogram. Stated otherwise, the electrocardiographic curve is similar to that produced when the left or the right ventricle is stimulated to contract artificially or spontaneously from an ectopic focus (extrasystole).

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11. Rothberger, C. J., and Winterberg, H.: Zur Diagnose der einseitigen Blockierung der Reizleitung in den Tawara'schen Schenkeln, Zentralbl. f. Herzkr. **5**:206, 1913; Experimentelle Beiträge zur Kenntnis der Reizleitungsstörungen in den Kammern des Säugetierherzens, Ztschr. f. d. ges. exper. Med. **5**:264, 1916.

12. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart, Phil. Tr. Roy. Soc., London, s.B **207**:221, 1916.

13. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, Heart **8**:229 (May) 1921.

14. Smith, F.: Experimental Observations on the Atypical Q-R-S Waves of the Electrocardiogram of the Dog, Arch. Int. Med. **26**:205 (Aug.) 1920; Further Observations on Experimental Lesions of the Branches of the Auriculoventricular Bundle of the Dog, ibid. **28**:453 (Oct.) 1921.

15. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, Ltd., 1920.

The following features of dogs and monkeys were thought to be the same as those of human beings so far as the levocardiogram and the dextrocardiogram were concerned: (1) The amplitude of the chief deflection is greater than normal, (2) the initial phases (main ventricular deflections) have an unusually long duration, and (3) the final deflection (T wave) is always opposite in direction to the chief initial deflection. Each curve is, as a whole, broadly diphasic.

Einthoven[16] first showed that the levocardiogram in modified form represents preponderance of the left ventricle and the modified dextrocardiogram preponderance of the right ventricle. The modifications are chiefly that the T wave is not necessarily directed opposite to the chief ventricular deflection. In bundle-branch block the QRS complex is usually of longer duration than in ventricular preponderance, and the main ventricular deflection is often notched. In clinical cases Hyman and Parsonnet[17] have shown that electrocardiographically left or right ventricular preponderance may change to right or left bundle-branch block.

In brief, "right bundle-branch block" is said to deform the ventricular complexes in the direction of the levocardiogram, the left extrasystole or the modified left ventricular preponderance, and "left bundle-branch block," in the direction of the dextrocardiogram, etc. These facts are easy to explain, at least so far as they affect the experimental animal. Section of the right bundle branch bars the passage of the excitation wave which reaches it from the auriculoventricular bundle. The same wave finds the pathway free to the left ventricle, whence the left preponderance. It then reaches the right ventricle by a detour, longer than normal, hence the widening of the electric ventricular group QRS and its abnormal notching. Finally, this deviation consequently produces a parallel deformation of the final ventricular phase (T wave), as if the excitation wave sprang first in the left ventricle, i. e., as in the left extrasystole.

Recently, Barker, Macleod and Alexander,[18] by electric stimulation of the exposed human heart, have thrown doubt on the accuracy of the interpretation as to which is the levocardiogram and which the dextrocardiogram in the case of the human being. They obtained curves exactly opposite to those previously obtained in animals. Later, Wilson,

16. Einthoven, W.: Le télécardiogramme, Arch. internat. d. physiol. **4**:132, 1906; Weiteres über das Electrokardiogramm, Arch. f. d. ges. Physiol. **122**:517, 1908.

17. Hyman, A. S., and Parsonnet, A. E.: Bundle-Branch Block: The Phenomenon of Its Development in Relation to Axis Deviation of the Heart, Arch. Int. Med. **45**:868 (June) 1930.

18. Barker, P. S.; Macleod, A., and Alexander, J.: Excitatory Process Observed in Exposed Human Heart, Am. Heart J. **5**:720, 1930.

MacLeod and Barker,[19] using semidirect leads in dogs in which one or the other bundle branch had been severed and the ventricles stimulated separately by an exploring electrode held close to their surface, produced results indicating that the common type of bundle-branch block, formerly called right bundle-branch block, is left bundle-branch block, and that the rare type is right bundle-branch block. Roberts, Crawford, Abramson and Cardwell,[20] in experiments in which they divided the bundle branches in cats' hearts, obtained both concordant and discordant curves in which when the right bundle branch was cut the chief initial deflection was downward in both types, but in lead 3 the deflection was upward in the discordant type. After cutting the left bundle branch, exactly opposite results were obtained. They concluded that in analyzing electrocardiographic curves the important lead to study in order to decide on the location of the lesion is lead 1. In human cases of bundle-branch block Nichol [21] found that in instances of right bundle-branch block the subclavian pulse was definitely delayed, and he concluded that the curves really signified left bundle-branch block. Wilson, Johnston, Hill, Macleod and Barker,[22] by means of serial precordial leads in patients with standard electrocardiographic curves largely similar to those formerly called left bundle-branch block (QRS of 0.12 second or more, narrow R deflections and broad S deflections in lead 1; narrow Q or S deflection in lead 3 synchronous with R of lead 1, and a broad upward deflection in lead 3 synchronous with S in lead 1), obtained curves in which the precordial leads from the right side of the precordium showed a very late chief upstroke and precordial leads from the left side of the precordium showed an early chief upstroke approximately synchronous with the peak of R in lead 1. These curves were strikingly similar to those which they obtained by the same method of leading after section of the right bundle branch in dogs. They concluded that electrocardiograms of the kind mentioned represent right bundle-branch block in man.

Unfortunately, as Mahaim [1] has so well shown, there have been few convincing histopathologic studies made of human hearts in cases in which during life bundle-branch block was thought to exist. In his

19. Wilson, F. N.; Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle-Branch Block, Am. Heart J. **7**:305 (Feb.) 1932.

20. Roberts, G. H.; Crawford, J. H.; Abramson, D. I., and Cardwell, J. C: Experimental Bundle-Branch Block in the Cat, Am. Heart J. **7**:505 (April) 1932.

21. Nichol, A. D.: The Interpretation of Lead Inversion in Bundle-Branch Block, Am. Heart J. **9**:72, 1933.

22. Wilson, F. N.; Johnston, F. D.; Hill, I. G. W.; Macleod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead 1, Am. Heart J. **9**:459, 1934.

critical review of the literature he found only 19 cases of this kind studied, and of these there were only 3 convincing cases and 1 probable case. In these 4 cases the expected lesions were found (on the basis of the old terminology). Mahaim himself most carefully studied histopathologically 7 cases of clinical bundle-branch block [23] (6 of the right and 1 of the left—observations V, VI, VII, VIII, IX, X and XII) and did not find lesions confined to one bundle branch alone in any. When "right bundle-branch block" was indicated electrocardiographically (observations V, VI, VII, VIII, IX and X) he found destructive lesions of the right branch and also of the anterior division of the left branch. In his single case of "left bundle-branch block" both branches were also involved. In connection with Mahaim's studies it is interesting to note that Wilson and Herrmann,[13] in an experiment with a dog in which the right bundle branch had been cut and later the anterior division of the left, found that before the latter cut was made the curves for the right branch block were of the concordant type, whereas those obtained after the second cut were of the discordant type and exactly similar to those in Mahaim's cases of human "right bundle-branch block," in which both the right bundle branch and the anterior division of the left branch were affected. Rothberger and Winterberger [11] had previously obtained similar curves experimentally in the same way.

Subsequently to Mahaim's study, Oppenheimer and Oppenheimer [24] presented in abstract the results of studies of 10 cases of clinical bundle-branch block and so-called arborization block. They claimed to have found lesions localized in the left branch in 5 cases of "right bundle-branch block," in the left branch in 4 cases of "arborization block," and in the right branch in 1 case of "left bundle-branch block."

Recently, in a case of so-called arborization block with slight left ventricular preponderance thoroughly studied by Mahaim,[25] he found extensive destructive lesions of both branches. To explain the failure of the appearance of auriculoventricular block he found conduction bundles leading from the upper, uninvolved portion of the posterior division of the left bundle branch and passing inward and downward in the septal myocardium, evidently carrying the impulses from the bundle of His to the ventricles. He concluded that "arborization block" is due to complete destruction of both bundle branches.

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23. We have not included observation XI since this appears to be a case of auriculoventricular block due to lesions of the two bundle branches.

24. Oppenheimer, B. S., and Oppenheimer E.: The Site of the Cardiac Lesion in Ten Cases of Intraventricular Block Including Bundle-Branch Block and Arborization Block, Tr. A. Am. Physicians **45**:427, 1930.

25. Mahaim, I.: Nouvelles recherches sur les lesions du faisceau de His-Tawara: Le bloc bilatéral manqué, nouvelle formeanatomique de bloc du cœur; à substituer au bloc dit "d'arborisations," Ann. de méd. **32**:347, 1932.

The great discrepancy in all of these works has one main lesson for us, viz., that more thorough and more accurate histopathologic studies are absolutely necessary to settle the questions of "bundle-branch block" and of "arborization block" for clinical cases. Our own experience coincides with that of Mahaim in that lesions of one bundle branch alone are rare. This is not difficult to explain, as will be seen when we come to consider the pathogenesis of "bundle-branch block." We believe that Mahaim [1] has definitely shown that previous conceptions of "bundle-branch block" in the human being were erroneous both as to the histopathologic basis of the electrocardiographic picture and as to the electrocardiographic criteria of bundle-branch lesions.

ELECTROCARDIOGRAPHIC ALTERATIONS IN BILATERAL BUNDLE-BRANCH BLOCK

In 1909 Barker and Hirschfelder [26] demonstrated by section of both bundle branches experimentally that complete auriculoventricular dissociation results from this mutilation. Eppinger and Rothberger [27] still more convincingly showed experimentally that transection of both bundle branches causes complete auriculoventricular dissociation, as does interruption of the main stem. Wilson and Herrmann [13] gave added information experimentally for such lesions. Their results were so striking and their conclusions so logical as to make them classic, and we cannot refrain from quoting them verbatim.

> We found that in bilateral bundle-branch block the ventricular complex might begin with right ventricular effects, indicating a right-sided pace-maker; it might begin with left ventricular effects, indicating a left-sided pace-maker; or it might be of relatively normal outline as in the instance described by Eppinger and Rothberger.[27] Providing, as we are led to believe, that only the specialized tissues possess the property of rhythmicity in high degree, the normal type of ventricular complex in bilateral bundle-branch block can result only from the simultaneous activity of two pace-makers, one in each branch of the bundle. We cut both divisions of the His-bundle in five experiments. In one of these, the ventricular complexes were of relatively normal form. In the others, occasional changes in the location of the pace-maker from one side to the other occurred, and these shifts were usually accompanied by complexes of transitional form . . . The experiments . . . convince us that complete heart block associated with ventricular complexes of varying form is usually due to bilateral bundle-branch block and not to a lesion of the main stem of the His-bundle.

That this is exactly true in cases of actual disease of both bundle branches is amply borne out in human cases in which histopathologic

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26. Barker, L., and Hirschfelder, A.: The Effects of Cutting the His Bundle Going to the Left Ventricle, Arch. Int. Med. **4**:193 (Oct.) 1909.

27. Eppinger, H., and Rothberger, C. J.: Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr. f. klin. Med. **70**:1, 1910.

studies have been made. Among the accepted cases of auriculoventricular block which we have already summarized, case 3 was an instance of auriculoventricular block with at first the curve called left bundle-branch block and later that called right bundle-branch block; case 4 showed the curve called left bundle-branch block in addition to auriculoventricular block; case 6 showed the curve called right bundle-branch block with two types of ventricular complexes suggesting two pacemakers in one branch distribution, and case 7 showed abnormal ventricular complexes of the so-called arborization type. In our case 2, after complete auriculoventricular block had become established, the electrocardiogram suggested the origin in one branch, since the curve might be called "incomplete right bundle-branch block" (fig. 5). In case 3, whenever auriculoventricular block was present there was variation in the electrocardiographic picture, but in general the tracings were those of "incomplete left bundle-branch block," suggesting, therefore, the site of the pace-maker in the distribution of the other bundle branch (figs. 12, 13 and 14).

Although it is probably true that lesions confined to the bundle branches are the usual cause of varying ventricular complexes, there is no reason why destructive lesions of the terminal portion of the bundle of His may not also produce such changes, as is demonstrated well in the case of Don, Grant and Camp,[3f] in which a mass of calcium destroyed the bundle at its bifurcation, and in the somewhat similar case of Yater and Willius.[28t]

28. In the following list the cases are distinguished by roman numerals: I. (*a*) Monrad-Krohn, G.: Le faisceau auriculo-ventriculaire dans le coeur humain, Arch. d. mal. du coeur **4**:350, 1911. II. (*b*) Koch, W.: Zur Anatomie und Physiologie der intrakardialen motorischen Zentren des Herzens, Med. Klin. **1**:109, 1912. III. (*c*) Mathewson, G. D.: Lesions of the Branches of the Auriculoventricular Bundle, Heart **4**:385, 1912-1913. IV. (*d*) Oppenheimer, B. S., and Williams, H. B.: Prolonged Complete Heart Block, Without Lesion of the Bundle of His and with Frequent Changes in the Idioventricular Electrical Complexes, Proc. Soc. Exper. Biol. & Med. **10**:86, 1913. V. (*e*) Cohn, A. E.: A Case of Transient Complete Auriculoventricular Dissociation, Showing Constantly Varying Ventricular Complexes, Heart **5**:5, 1913-1914. VI. Hoffmann[8y] (1914). Mönckeberg[8n] (1916). VII. (*f*) Christian, H. A.: Transient Auriculoventricular Dissociation with Varying Ventricular Complexes Caused by Digitalis, Arch. Int. Med. **16**:341 (Sept.) 1915. VIII. (*g*) Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, ibid. **16**:1008 (Dec.) 1915. IX. Biedl and Riehl[8d] (1916). X. (*h*) Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, Arch. Int. Med. **18**:830 (Dec.) 1916. XI. (*i*) Krumbhaar, E. B.: Transient Heart Block—Electrocardiographic Studies, ibid. **19**:750 (May) 1917. XII. (*j*) Wilson, F. N., and Robinson, G. C.: Heart Block: I. Two

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Many clinical cases in which no detailed histopathologic studies were made are now on record in which the form of the ventricular complexes in the presence of auriculoventricular block was of the bundle-branch type.[28] In a number of these, in tracings made at different times or in the same tracing, there were shifts abrupt or gradual, in the form of the ventricular complexes from the right to the left bundle-branch type or intermediate forms. In some of these cases the idioventricular rhythm was rapid, indicating probably an irritative as well as a destructive lesion in the branch from which the impulses originated. White and Viko [28m] found that in 154 cases of complete heart block there was electrocardiographic evidence of intraventricular block in 56 per cent. In a clinical study of 37 cases Willius [28n] noted similar abnormal ventricular complexes in 43 per cent and varying forms of QRS complexes in 9 cases, "indicating multiple foci of impulse production in the ventricles." Among 35 of 43 patients with complete heart block who were followed, Ellis [28m'] noted "intraventricular block" in 5 and "bundle-branch block" in 3. Scherf and Schott [28h'] had 7 cases of shifting pace-makers in association with auriculoventricular block. Coehlo [28o'] mentioned 30 cases of auriculoventricular block in which the ventricular complexes varied from time to time in duration and voltage; he discussed the question whether such modifications are due to changes in intraventricular conduction with a single pace-maker or to changes in the site of the pace-maker, and he concluded that the latter is the case. In an analysis of 395 cases of "bundle-branch block," Graybiel and

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Cases of Complete Heart-Block Showing Unusual Features, ibid. **21**:166 (Jan.) 1918. XIII. (*k*) Winterberg, H.: Beitrag zur Kenntnis der Störungen in der Reizübertragung des menschlichen Herzens und der Anfälle bei Adams-Stokes'schen Symptomenkomplex, Ztschr. f. d. ges. exper. Med. **8**:132, 1919. XIV. (*l*) Korns, H. M.: Delayed Conduction Through the Right and Left Branches of the Atrioventricular Bundle, Arch. Int. Med. **30**:158 (Aug.) 1922. XV. Meyer and Oberling [8g'] (1923). XVI. (*m*) White, P. D., and Viko, L. E.: Clinical Observations on Heart Block, Am. J. M. Sc. **165**:659, 1923. XVII. (*n*) Willius, F. A.: A Clinical Study of Complete Heart-Block, Ann. Clin. Med. **3**:129, 1924. XVIII. (*o*) Géraudel, E., and Giroux, R.: Le syndrome d'Adams-Stokes et sa pathogénie, Presse méd. **34**:258, 1926. XIX. (*p*) Géraux, E.; Bénard, R., and Hillemand, P.: Un second cas de bradyrythmie ventriculaire par sténose de l'artère du ventriculonecteur, Arch. d. mal. du coeur **19**:229, 1926. XX. (*q*) Géraudel, E.; Bénard, R.; Gautier, C., and Heyman: Un troisième cas de bradyrythmie ventriculaire par sténose de l'artère du ventriculo-necteur (syndrome d'Adams-Stokes), Presse méd. **35**:1129, 1927. XXI. (*r*) Gilchrist, A. E., and Cohn, A. E.: Ventricular Complexes in Complete Heart Block, Am. Heart J. **3**:146, 1927. XXII. (*s*) Robb, J. S.: Heart Block Associated with Multiple Ventricular Pace-Makers, Medical and Surgical Year-Book, Physicians Hospital of Plattsburg, 1929, vol. 1, p. 279. XXIII. (*t*) Yater, W. M., and Willius, F. A.: Heart Block Showing Multiple Transitions Associated with Convulsive Syncope: Report of a Case with Detailed Histopathological Study,

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Sprague [28w'] found 17 instances of complete and 20 of partial auriculoventricular block. In a similar study King [28x'] noted the frequent coexistence of "bundle-branch block" and varying degrees of auriculoventricular delay or block. Among 155 cases of "bundle-branch block" there were 36 instances of complete auriculoventricular block, and in 5 of these there was evidence of shifts of the pace-maker from one side to the other.

Gilchrist and Cohn,[28r] in reporting 2 cases of complete auriculoventricular dissociation accompanied by the occasional spontaneous appearance of a succession of complexes, each being intermediate in form as compared with its neighbors and varying in type between the levocardiogram and the dextrocardiogram, stated that it is not justifiable to assume that clinical curves displaying such peculiarities indicate necessarily bilateral organic lesions of the bundle branches since the same effects might as readily be produced by functional depression of conductivity as by digitalis. They pointed out, as did Wilson and Herrmann,[13] that the effect of a lesion which delays without completely interrupting the passage of an impulse through one of the main divisions of the bundle will be an alteration in the ventricular deflection and that this will consist in a shift in the time relations of right and left ventricular effects. By the algebraic summation of levocardiogram and dextrocardiogram in varying time relations to each other, as previously done by Wilson and Herrmann,[13] Gilchrist and Cohn found that it was possible to reproduce the transitional complexes for each of their 2 cases. They concluded

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Am. Heart J. **4**:280, 1929. XXIV. Géraudel, Brodin and Lereboullet [8k'] (1929). XXV. (*u*) Bloom, B., and Perlow, S.: Complete Heart-Block Associated with Rapid Ventricular Rate: Report of Two Cases, Am. Heart J. **5**:486 (April) 1930. XXVI. (*v*) Géraudel, E., and Lereboullet, J.: Syndrome d'Adams-Stokes à évolution rapide par thrombose de la coronaire droite et de l'artère du ventriculonecteur, Paris méd. **2**:25 (July 5) 1930. XXVII. (*w*) Géraudel, E.: Etude électrocardiographique et anatomique d'un cas de syndrome d'Adams-Stokes, Arch. d. mal. du coeur **23**:704 (Nov.) 1930. XXVIII. (*x*) Grassberger, A.: Klinische, elektrokardiographische und histologische Untersuchung eines Falles von Adams-Stokes'scher Erkrankung, Ztschr. f. klin. Med. **112**:388, 1930. XXIX. (*y*) Henkel, G.: Anfallsweise Störungen der Reizbildung und Reizleitung im menschlichen Herzen, Deutsches Arch. f. Klin. Med. **167**:244, 1930. XXX. (*z*) Hall, D.: Two Unusual Electrocardiograms, Proc. Roy. Soc. Med. **24**:1512, 1931. XXXI. (*a'*) Mohler, H. K.: Bundle-Branch Block: Its Diagnosis and Relation to Other Cardiac Disturbances, M. Clin. North America **14**:885, 1931. XXXII. (*b'*) Padilla, T., and Cossio, P., Jr.: Disociación auriculoventricular a mayor frecuencia ventricular por interferencia de dos ritmos, Semana méd. **1**:1306 (May 14) 1931. XXXIII. (*c'*) Carter, E. P., and McEachern, D.: Recurrent Complete Heart Block: Report of a Case Associated with Transient Bundle-Branch Block and Normal Conduction Between Attacks, Bull. Johns Hopkins Hosp. **49**:337 (Dec.) 1931. XXXIV. Mahaim [1] (1931), cases IV and XI. XXXV. (*d'*) Parade, G. W., and Voit, K.: Zur Pathologie und Therapie der Adams-

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that the most likely explanation consists in a change in leadership of the predominant pace-maker from one side of the heart to the other. We agree with this conception, but we believe also that the site of the pace-maker may change from time to time in the distribution of the same bundle branch, and in addition that after leaving the pace-maker there may be a slight variation in the path of the excitation wave from time to time.

The explanation of the supraventricular form of the ventricular complexes when complete auriculoventricular block is due to interruption of both bundle branches is more open to debate. The complexes in our case 1 might be considered to be more or less of this form (fig. 1). It is necessary, according to the theory of Wilson and Herrmann,[13] to assume that there are two pace-makers, one in each bundle branch, generating synchronously impulses which pass with equal facility down their respective arborizations and produce the algebraic summation of exact superimposition of levocardiogram and dextrocardiogram as in normal auriculoventricular conduction. This may be possible, but it seems to us to be improbable. We are inclined to the theory that there is only one predominating pace-maker at any one time, and that when the complexes are of the so-called supraventricular form the impulses from this pace-maker pass rather directly from the pace-maker to the Purkinje network of the opposite ventricle; whereas, when the complexes are of the type of intraventricular block, there is a less direct passage of the impulse from one ventricle to the other. In a somewhat similar way

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Stokes'schen Krankheit, Deutsche med. Wchnschr. **57**:629 (April 10) 1931. XXXVI (*e'*) Géraudel, E.: De syndrome de Adams-Stokes, endartérite à tendance oblitérante de la coronaire droite et de l'artère du ventriculo-necteur, Arch. d. mal. du coeur **24**:605 (Oct.) 1931. XXXVII. (*f'*) Géraudel, E.; Girard, J., and Simonin, J.: Mutilation du faisceau de His an niveau de sa moitié gauche, absence de déformation du ventriculo-gramme, Ann. d'anat. path. **9**:715 (July) 1932. XXXVIII. (*g'*) Condorelli, L.: Schenkelblock durch Läsion des Tawaraknotens, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1932, p. 292. XXXIX. (*h'*) Scherf, D., and Schott, A.: Ueber die Ursache des Formwechsels automatischer Kammerschläge beim vollständigen Herzblock, Klin. Wchnschr. **11**:945, 1932. XL. (*i'*) Hahn, L.: Initiale Querdissoziation mit Adams-Stokes'schen Anfällen bei akutem Myokardinfarkt, Ztschr. f. Kreislaufforsch. **24**:129 (March) 1932. XLI. (*j'*) Coelho, E.: Tachycardie ventriculaire au cours de la maladie d'Adams-Stokes par dissociation auriculoventriculaire, Arch. d. mal. du coeur **25**:232 (April) 1932. XLII. (*k'*) Elliott, A. H., and Nuzum, F. R.: Bundle-Branch Block with Periods of Normal Intraventricular Conduction: Report of an Unusual Case, Am. Heart J. **7**:680 (June) 1932. XLIII. (*l'*) Walser, J.; Lenégre, J., and van Bogaert, A.: Un cas d'atteinte diffuse du système autonome du coeur, Arch. d. mal. du coeur **25**:410 (July) 1932. XLIV. Grant and Camp[3e] (1932). XLV. Don, Grant and Camp[3f] (1932). XLVI. (*m'*) Rosenthal, S. R.: Branch Arborization and Complete Heart-Block, Arch. Int. Med. **50**:730 (Nov.) 1932. XLVII. (*n'*) Ellis, L. B.: Studies in Complete Heart Block: II. A

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we may explain why in our case 2, after the establishment of 2 to 1 auriculoventricular block, the ventricular complexes for a time were of the supraventricular form (fig. 6), although previously they were of the "right bundle-branch block type." Here we may assume that every other impulse failed to come through either bundle branch, but that, one branch being more affected than the other, only the one branch conducted the alternate impulses; these impulses, however, passed directly through the septum from the conducting branch and entered the Purkinje network of the opposite ventricle below the point of obstruction in the branch. After the establishment of complete block, of course, the pace-maker undoubtedly resided in one bundle branch below the point of interruption of its continuity. The impulses then apparently passed more indirectly to the Purkinje network of the opposite ventricle (fig. 7). In our case 3 we may note also that whenever there was sinus rhythm or only partial auriculoventricular block (fig. 3) there seemed to be some delay in the passage of the impulse down one bundle branch (presumably the right on the basis of the old terminology) whereas whenever complete auriculoventricular block existed, the site of the pace-maker was apparently in the same bundle branch below its point of damage (figs. 12, 13 and 14), and from there the excitation wave reached the opposite ventricle by a detour.

Our theory has some basis in recent anatomic studies. Cardwell and Abramson,[29] by injections of india ink into the conduction system and subsequently studying the microscopic sections, have demonstrated

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Clinical Analysis of 43 Cases, Am. J. M. Sc. **188**:225, 1932. XLVIII. (*o'*) Coelho, E.: Le mécanisme de la variation de forme des complexes ventriculaires dans le block complet du coeur, Arch. d. mal. du coeur **25**:695 (Nov.) 1932. XLIX. (*p'*) Katz, L. N.; Hamburger, W. W., and Rubinfeld, S. H.: Partial Bundle-Branch Block, Am. Heart J. **7**:753 (Aug.) 1932. L. (*q'*) Friedmann, H.: Ein Beitrag zur Frage der Reizleitungsstörung des Herzens bei Diphtherie, Wien. med. Wchnschr. **82**:1231 (Sept. 24) 1932. LI. (*r*) Natin, I.: El bloqueo aurículo-ventricular en la difteria, Semana méd. **2**:865 (Sept. 29) 1932. LII. (*s'*) Freifrau, A.: Ueber einen Fall von wechselnder peripherer Leitungsstörung des Herzens mit wechselnder Form der Kammerkomplexes, Ztschr. f. Kreislaufforsch. **10**:337, 1933. LIII. (*t'*) Garcia, V. G.: Bloqueo de la rama derecha del fasciculo de His, con bloqueo intermitente auriculoventricular, Progresos de la clín. **41**:368 (June) 1933. LIV. (*u'*) Géraudel, E.; Laignel-Lavastine, P. M., and Boquien, Y.: Un cas d'Adams Stokes; longes pauses ventriculaires; tracés de transition entre les deux types de dissociation, Arch. mal. d. coeur **26**:1, 1933. LV. (*v'*) Pareja, J. M.: Période de restauration supernormale dans une dissociation auriculo-ventriculaire complète, Arch. d. mal. du coeur **26**:395, 1933. LVI. (*w'*) Graybiel, A., and Sprague, H. B.: Bundle-Branch Block: An Analysis of Three Hundred and Ninety-Five Cases, Am. J. M. Sc. **185**:395 (March) 1933. LVII. (*x'*) King, J. T.: Bundle-Branch Block: A Case Analysis with Especial Reference to Incidence and Prognosis, ibid. **187**:149 (Feb.) 1934.

29. Cardwell, J. C., and Abramson, D. I.: The Atrioventricular Conduction System of the Beef Heart, Am. J. Anat. **49**:167, 1931.

in the beef heart Purkinje fibers throughout the myocardium, as well as in the subendocardium and in the septal region, apparently connecting the subendocardial network on the two sides of the septum. A similar study with the same result has been made independently by Wahlin;[30] by means of serial sections and reconstruction models after injections of india ink he demonstrated the presence of an intraseptal Purkinje network passing between the two sides of the septum. Although such an intramyocardial network and such a transseptal connection have not been ascertained for the human heart because injections of india ink are not satisfactory and because the Purkinje fibers are too similar morphologically to the myocardial fibers to be recognizable microscopically, it seems logical to assume that such a network and such connections exist. Mahaim[25] claimed to have observed a special pathway of this kind in a human heart, and Géraudel[31] hinted that direct connections exist between the main divisions of the conduction system and the myocardium in human cases. Rothberger[32] has also subscribed to a similar conception. The ventricular complexes will vary, therefore, according to the directness or indirectness with which the excitation wave spreads from its new pace-maker to the opposite ventricle. If the spread is directly through the septum to the Purkinje network of the opposite ventricle the complexes should be of the supraventricular form since both ventricles are activated almost simultaneously; if the spread is indirectly through the septal myocardium the curves should suggest intraventricular block of incomplete bundle-branch form, and if the spread is first through one branch distribution before the other ventricle is activated the curves should suggest more the picture of complete bundle-branch block.

PATHOGENESIS OF "BUNDLE-BRANCH BLOCK"

By far the most common cause of bundle-branch lesions is coronary arterial sclerosis.[33] This preponderance is not so great in lesions of the main stem of the conduction system (table). In the pathogenesis of bundle-branch lesions the next most common factor is probably endocarditis extending downward from the aortic or mitral valve to involve

30. Wahlin, B.: Die interventrikulären Verbindung im Reizleitungssystem des Herzens, Upsala läkaref. förh. **38**:1, 1932.

31. Géraudel, E., and Gautier, C.: Syndrome d'Adams-Stokes por nécrose transverse du ventriculo-necteur consécutive à une endartérite oblitérante de son artère, Ann. d'anat. path. **8**:339 (April) 1931. Géraudel.[28k'] Géraudel and Lereboullet.[28v] Géraudel.[28w] Géraudel.[28e'] Géraudel, Girard and Simonin.[28f']

32. Rothberger, C. J.: Beitrag zur Kenntnis der intraventriculären Leitungsstörungen und zur Therapie des "Arborisation Block," Ztschr. f. d. ges. exper. Med. **87**:763, 1933.

33. Mahaim.[1] Scherf and Schott.[28h'] White and Viko.[28m] Willius.[28n] Ellis.[28n'] Coelho.[28o'] Graybiel and Sprague.[28w'] King.[28x']

the left branch, but this cause is rare compared with the arterial etiology, and other causes are still more rare. Of the 21 cases of bundle-branch lesions associated clinically either with auriculoventricular block or unilateral bundle-branch block only which have been accepted by us from the literature as satisfactory from the standpoint of the histopathologic examination, coronary arterial disease was undoubtedly the only etiologic factor in 14, and in several others it was certainly an important factor in addition to endocarditis.

Mahaim [1] has explained well why cases of pure unilateral bundle-branch block must be very rare. The reason lies in the vascularization of the conduction system, which has been studied by several capable investigators.[34] The auriculoventricular node and bundle are supplied with blood almost entirely by one special artery, the ramus septi fibrosi or first posterior perforating artery, which passes forward into the auriculoventricular septum from the origin of the posterior descending or interventricular artery just at the point posteriorly where the two auricles and ventricles meet. In approximately 90 per cent of hearts this is a branch of the right coronary artery while in 10 per cent it is a branch of the left coronary artery, from the posterior extremity of its left circumflex branch, this artery then passing downward as the posterior descending artery. The anterior descending or interventricular artery may give a minor portion of the blood supply of the auriculoventricular bundle, especially in its anterior portion. As a rule, the origin of the bundle branches also takes its main vascularization from this ramus septi fibrosi, but there are numerous variations. The vascular supply of the bundle branches is less positively known than that of the auriculoventricular node and bundle, but there is a general more or less definite arrangement. The arteries arise from the anterior and posterior descending or interventricular arteries and perforate the interventricular septum, passing toward its middle, where they anastomose to a certain extent. The left bundle branch, being spread out over the subendocardial surface of the left side of the septum and divided usually into an anterior and a posterior division or ramification, has its blood supply both from the perforating septal branches of the anterior and from

34. (*a*) Hass, G.: Ueber die Gefässversorgung des Reizleitungssystems des Herzens, Anat. Hefte **43**:629, 1911. (*b*) Tandler, J.: Anatomie des Herzens, Jena, Gustav Fischer, 1913. (*c*) Gross, L.: The Blood Supply to the Heart, New York, Paul B. Hoeber, Inc., 1921. (*d*) Mouchet, A.: Les artères coronaires du coeur chez l'homme, Paris, Norbert Maloine, 1922. (*e*) Crainicianu, A.: Anatomische Studien über die Koronararterien und experimentelle Untersuchungen über ihre Durchgängigkeit, Virchow Arch. f. path. Anat. **238**:1, 1922. (*f*) Spalteholz, W.: Die Arterien der Herzwand, Leipzig, S. Hirzel, 1924. (*g*) Géraudel, E.: L'artère de l'atrionecteur: artère du noeud de Keith-Flack, Presse méd. **33**:1283 (Sept. 26) 1925.

those of the posterior descending artery. In a general way the anterior perforating arteries supply the anterior division of the left bundle branch, the posterior perforating arteries the posterior division. The vascularization of the right bundle branch, a threadlike fasciculus, is not so definitely known, but is most probably almost entirely derived from the perforating septal arteries of the anterior descending artery except, perhaps, in its terminal portion, which may receive some of its blood supply from the lower posterior perforating arteries. The upper third of the branch is probably supplied mainly by the two uppermost anterior perforating arteries and the middle third by a special branch of the second perforating artery, the ramus limbi dextri (Gross [34c]). This same special artery probably nourishes most of the lower third of the branch. The anastomoses between the anterior and posterior perforating arteries are probably very fine and not particularly effective, as has been shown so well by Crainicianu [34e] for sudden obstruction. With slow obliteration these anastomoses are probably more efficacious in maintaining an adequate blood supply than with sudden occlusion.

Thus, it is seen that the blood supply of the auriculoventricular node and bundle and of the posterior division of the left bundle branch comes mainly from the perforating septal arteries of the posterior descending or interventricular artery (in 90 per cent of cases a branch of the right coronary artery) whereas the blood supply of the right bundle branch and of the anterior division of the left branch is almost entirely derived from the perforating septal branches of the anterior descending or interventricular artery.

From these facts it may be deduced that since obliterating vascular disease affects most often and most severely the anterior descending artery, especially high in its course, the right bundle branch and the anterior division of the left branch are simultaneously affected, and more often than other parts of the conduction system, by the resulting reduction of blood supply. The electrocardiographic alterations would therefore be a combination of both right and left bundle-branch effects, as Mahaim [1] has demonstrated. If the posterior descending artery is mainly affected by obliterating vascular disease (a rare event) only the posterior division of the left bundle branch will be seriously undernourished, and there should be only minor alterations of the ventricular complexes. An occlusive lesion of the right circumflex artery (or in an occasional case of the left) might result in fibrosis of the auriculoventricular node or bundle and the origin of the bundle branches with disturbance in auriculoventricular conduction. Obliteration of both the anterior and the posterior descending arteries might result in severe alterations of both bundle branches and therefore in disturbances of auriculoventricular conduction.

Our case 1 is undoubtedly an instance of the latter condition. There was more or less generalized coronary sclerosis, most advanced in the anterior descending artery, but without total occlusion at any point. High-grade fibrosis of both bundle branches resulted. In our case 2 the cause of the fibrotic lesions of both bundle branches was undoubtedly also diminution of the blood supply of the branches, but, in this instance, from widespread sclerosis of the smaller intramyocardial coronary arteries. Case 3 was less definite from the standpoint of etiology, but here again it was probably an instance of vascular disease.

Endocarditis produces disturbance of conduction probably only when aortic or mitral lesions extend to the mural endocardium of the left side of the interventricular septum and involve those portions of the conduction system which are located in the left ventricle. The result would most often be a disturbance of auriculoventricular as well as left bundle-branch conduction, since the bundle of His is most apt to be involved, probably with a portion of the origin of the left bundle branch. It would be rare indeed to have the latter seriously affected without the bundle of His being affected at the same time. In contradiction to these statements it is interesting to note that in Kauf's [8h] case of clinical right bundle-branch block the lesion proved to be a fibrous one of the origin of the right bundle branch, although there was rheumatic aortic stenosis with calcification extending from the aortic valve down on to the left side of the septum. Tricuspid endocarditis is so unusual that involvement of the auriculoventricular bundle or the right bundle branch by endocarditis must be extremely rare. Tumors of the heart, which are not common, gummas, fibrous scars and intracardiac aneurysms in the interventricular septum apparently rarely involve a bundle branch sufficiently to interrupt completely its continuity. Three cases of auriculoventricular block have been reported in which the bifurcation of the bundle of His and the origins of the bundle branches were destroyed by fibrocalcareous lesions and in which electrocardiograms had shown also bundle-branch block with or without varying ventricular complexes (case of Hoffmann and Mönckeberg [8y]; case of Yater and Willius [28t]; case of Don, Grant and Camp [3f]).

MORBID ANATOMY OF THE CONDUCTION SYSTEM

Serious damage of the conduction system may result from coronary arterial disease long before complete occlusion, slow or sudden, produces a myocardial scar or infarct. The ultimate effect of progressive arterial disease on the conduction system is fibrous replacement, just as it is the ultimate result on the myocardium. In our cases 1 and 2 the fibrous replacement was confined to the conduction system, in particular to the bundle branches, and in case 3 the bundle branches were also

seriously affected whereas the myocardium was very moderately involved. This preponderance of involvement of the conduction system over that of the myocardium suggests that the former, like nerve tissue, is more susceptible to reduction of blood supply and anoxemia. The fact that there is a common vascular supply for the conduction system and the myocardium speaks for this conclusion. Other authors have noted this peculiarity, and long ago Mönckeberg [35] and Aschoff [36] commented on the limitation of pathologic changes to the conduction system in certain cases. Mönckeberg [37] noted that there might be fatty degeneration of the main portion of the conduction system without such involvement of the myocardium and vice versa. Such fatty degeneration of the conduction system does not result in heart block but possibly may cause sudden death.[38] Mönckeberg, after studying a case of heart block with fibrosis of the bundle branches, called such a condition *"selbständige Pathologie des Atrioventrikularsystems."*

Wearn [39] demonstrated that the number of capillaries per square millimeter in the conduction system is approximately only half of their number in the ventricular myocardium. This difference may be due to the difference in function of the two tissues, the one the main function of which is contractility requiring a larger blood supply than the one the main function of which is conduction. At the same time, this relative paucity of capillaries in the conduction system may account for the apparently greater susceptibility of this tissue to reduction in blood supply.

Perhaps, in our cases fibrous changes would have developed later in the myocardium if the patients had not died so soon in Adams-Stokes attacks. Perhaps also, if more histopathologic examination of the conduction system were made in cases of degenerative heart disease (hypertensive and arteriosclerotic) lesions would be frequently found even with minor electrocardiographic changes. Death may occur in such cases from congestive heart failure or coronary thrombosis before these changes become so great as to cause serious disturbances of conduction.

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35. Mönckeberg, J. G.: Zur Pathologie des Atrioventricularsystems und der Herzschwäche, Berl. klin. Wchnschr. **46**:45, 1909. Mönckeberg.[8h] cases 67 and 68. Mönckeberg,[8n] case 5.

36. Aschoff: Referat über die Herzstörungen in ihren Beziehungen zu den spezifischen Muskelsystemen des Herzens, Verhandl. d. deutsch. path. Gesellsch. **14**:3, 1910.

37. Mönckeberg, J. G.: Herzschwäche und plötzlicher Herztod als Folge von Erkrankungen des Atrioventrikularsystems, Ergebn. d. allg. Path. u. path. Anat. **14**:1, 1910.

38. Nuzum, F.: Fatty Infiltration (Lipomatosis) of the Auriculoventricular Bundle of His, with Sudden Unexpected Death, Arch. Int. Med. **13**:640 (April) 1914.

39. Wearn, J. T.: The Extent of the Capillary Bed of the Heart, J. Exper. Med. **47**:273, 1928.

TIME OF ONSET AND DEGREE OF CONDUCTION BLOCK

An interesting problem concerns itself with the question of how soon conduction disturbances occur when the vascularity of the conduction system is reduced. Géraudel [28w] expressed the belief that there may be complete inability of the bundle of His to conduct before any organic changes appear. His conclusion is based, however, on incomplete studies, as before mentioned. We do not think that in cases of permanent block of either the auriculoventricular bundle or the bundle branches conduction disturbances occur before there is considerable organic alteration. We do think, however, that serious difficulty of conduction may occur before the bundle or its branches are completely interrupted by organic lesions. This concept is demonstrated by our cases 2 and 3. In case 2 there was only moderate fibrosis of the right bundle branch, yet this bundle apparently did not conduct in its upper third. Parenthetically, this case might be used as an argument by those who have accepted the newer terminology for "bundle-branch block," since there was a large upright R wave in lead 1 and a deep S wave in lead 3 before auriculoventricular block developed, and the left bundle branch was much more seriously damaged than the right. In case 3 there was apparently not complete interruption of either bundle branch, yet at times there was complete auriculoventricular dissociation as well as electrocardiographic evidence of "bundle-branch block." In this case it was impossible to say which bundle branch was the more seriously damaged. Nutritional disturbances, toxic depression and vagal influences might each or all affect the remaining apparently healthy portion of the branches and depress their function permanently or paroxysmally more than the organic changes alone would. Both toxic and vagal influences on conduction have been repeatedly observed.[40] These factors would explain the shifts from partial or complete auriculoventricular block to sinus rhythm and back again, as in our case 3, and the paroxysmal auriculoventricular block early in the course of case 2. On the other side of this question are the cases which show that only a few remaining healthy fibers of the conduction system are sufficient to maintain normal conduction.

SUMMARY AND CONCLUSIONS

1. Three cases of auriculoventricular heart block due to lesions confined to both bundle branches are reported with detailed histopathologic studies. The pathogenesis was probably coronary arterial disease in all.

2. Such lesions of the bundle branches are probably a common, if not the commonest, cause of auriculoventricular heart block.

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40. Winterberg, H.: Zur Kenntnis und Analyse der periodischen Herztätigkeit beim Menschen, Ztschr. f. d. ges. Exper. Med. **10**:113, 1919.

3. The heart may appear grossly normal, with or without gross evidence of coronary arterial disease. The morbid anatomy is usually that of a fibrous replacement which does not necessarily completely destroy the continuity of the bundle branches. Microscopically as well as grossly, the myocardium may appear normal or relatively little affected. This fact indicates that the conduction system is more susceptible to diminution of blood supply than the myocardium is, since there is a common blood supply. If the patient lived longer, similar changes might develop in the myocardium.

4. The freedom of the auriculoventricular node and bundle from similar lesions in such cases is due to the fact that their blood supply comes from a source different from that of the blood supply of the bundle branches and from a portion of the coronary arterial tree less often and less severely affected by degenerative changes.

5. Lesions confined entirely to one bundle branch are apparently rare because of the common source of the blood supply of the right bundle branch and the anterior division of the left bundle branch from the anterior descending artery, which is most often and most seriously affected by degeneration.

6. The form of the ventricular complexes is frequently suggestive of "bundle-branch block," and variation in the form of these complexes is common. These variations suggest a shift in the site of the pace-maker, sometimes from one side of the septum to the other. The ventricular complexes may be of supraventricular form, however; and then there are either two pace-makers, one in each bundle branch, generating impulses simultaneously or, more probably, a single pace-maker in one or the other branch sending impulses directly through the interventricular septum into the Purkinje network of the contralateral ventricle as well as into that of the homolateral ventricle.

7. There may be a variability from time to time in the degree of auriculoventricular dissociation, indicating that there are other factors involved besides the organic lesions of the bundle branches.

8. In such cases as these, death frequently occurs in an Adams-Stokes attack.

9. More frequent and more careful histopathologic studies of the entire recognizable conduction system are urgently needed because of the uncertainties at present involved in the interpretation of electrocardiographic alterations.

ERYTHROCYTE FRAGILITY IN PNEUMONIA

ROBERT J. NEEDLES, M.D.
DETROIT

One of the chief causes of death in the valley of the Amazon is lobar pneumonia. This is due in part to the low resistance of the native, a factor which has been discussed in a previous publication.[1] In an industrial enterprise such as the Ford rubber plantation, the control of this disease assumes importance second, perhaps, only to the control of malaria and to general sanitation. In the hospital of the company, located at Boa Vista, Rio Tapajóz, Brazil, there was an admirable opportunity to study tropical pneumonia, and therefore I undertook a series of investigations in an effort to understand the disease more fully.

In the course of the investigations I had occasion to make some tests for the fragility of the erythrocytes. I expected, particularly in cases of jaundice, that the resistance of the red blood cells might become less, but instead in many cases it increased. The results were deemed sufficiently interesting to be reported separately.

A survey of the literature has revealed that little interest has been shown in the study of the fragility of the erythrocytes in cases of pneumonia. The resistance of human red blood corpuscles to hypotonic solutions of sodium chloride has been the subject of considerable investigation in the past. These studies, however, have usually been conducted in instances in which blood dyscrasia, such as hemolytic icterus or purpura haemorrhagica occurred. The test is described in several books on clinical laboratory methods,[2] but in none is any mention made of its usefulness in other than hematologic conditions. One reference to the resistance of the red blood cells in pneumonia was found. Petrányi [3] used such an examination in a series of cases of pneumonia in children. His results, while given in a different scale, parallel ours; that is, in pneumonia he found that the resistance of the erythrocytes to hemolysis was increased.

From the Medical Department of the Companhía Ford Industrial do Brazil and the Department of Laboratories, the Henry Ford Hospital.

1. Needles, R. J.: Health Problems in the Amazon Valley, Science **78**:532 (Dec. 8) 1933.

2. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1930. Kolmer, J. A., and Boerner, F.: Approved Laboratory Technic, New York, D. Appleton & Company, 1931. Stitt, E. R.: Practical Bacteriology, Blood Work and Animal Parasitology, Philadelphia, P. Blakiston's Son & Co., 1927. Nicholson, D.: Laboratory Medicine, Philadelphia, Lea & Febiger, 1930.

3. Petrányi, Győző: Erythrocyte Resistance in Various Stages of Pneumonia, Orvosi hetil. **72**:1180, 1928.

The basis for hemolysis of the red blood cells in hypotonic saline solution lies in the osmotic phenomena of such a relationship. The salt concentration of normal blood serum is from 0.8 to 0.9 per cent, and that of the human erythrocyte is about the same strength. When placed in solutions of less concentration than this the corpuscles tend to absorb water from the surrounding fluid medium in an effort to adjust the salt concentration toward an equilibrium. When the amount of salt in the medium is sufficiently low, the erythrocytes absorb so much water that they rupture. This rupture releases hemoglobin into the surrounding fluid, and when this is grossly evident, hemolysis or laking of the blood is said to have taken place.

TECHNIC

In most textbooks of laboratory technic directions are given for performing a fragility test. A 0.5 per cent solution of sodium chloride is used, and by adding this standard to graduated amounts of water a series of solutions varying from 0.26 to 0.48 per cent is produced. This method is satisfactory but subject to error.

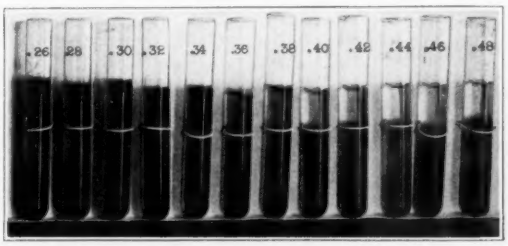

Fig. 1.—Photograph illustrating the appearance of normal fragility. A faint tinge of beginning hemolysis may be seen at a dilution of 0.44 per cent, which becomes progressively more marked and is complete at 0.36 per cent.

In the tests reported here a series of accurate solutions of sodium chloride have been made by weighing the precise amount of salt necessary on an analytic balance, the solutions being made in volumetric flasks. These standards are made in 1 liter amounts, which is sufficient for many examinations and assures continuously accurate salt concentrations.

In performing the test a set of twelve tubes is made up. These may be of any size, though the convenient Wassermann tube (75 by 15 mm.) gives good results. Into each of these is placed from 3 to 4 cc. of saline solution, starting with a concentration of 0.26 per cent in the first tube and running up to 0.48 per cent in the twelfth tube, the interval between being 0.02 per cent. The rack of tubes being thus prepared, 2 cc. of venous blood is withdrawn from the patient in a clean dry syringe, and 1 drop of blood is quickly placed in each tube. The tubes are then shaken gently, or inverted to insure adequate mixing, and put aside for two or three hours to allow the contents to settle. After this period it is possible to read the results of the test, examining the tubes by transmitted light. The first appearance in a tube of a yellowish or brownish tint in the supernatant fluid is said to mark the point of beginning hemolysis. Normally this

occurs with a concentration of saline solution of from 0.44 to 0.46 per cent. When after a tube is shaken no more sediment can be demonstrated, hemolysis is said to be complete. Normally this occurs with a concentration of 0.36 per cent, and the normal fragility of erythrocytes is from 0.36 to 0.44 per cent (fig. 1).

OBSERVATIONS

A series of examinations of 100 normal Brazilians of this region, who were of mixed races, including varying percentages of Negro, Indian and white blood, was made. In these persons the fragility of the erythrocytes was found to be from 0.36 to 0.44 per cent, stated in terms of accurately weighed solutions of sodium chloride.

The study embraced a series of 30 cases of typical lobar pneumonia. From these 6 cases were selected for description and graphic representation of temperature and erythrocyte fragility. Cases of different degrees of severity were selected in order to demonstrate the close adherence of the values for fragility to the severity of the illness of the patient.

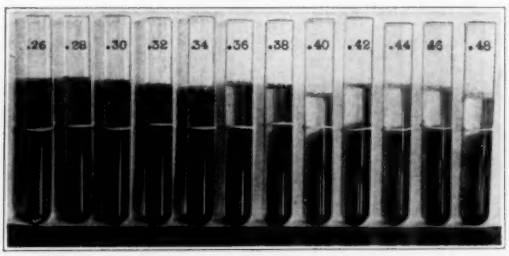

Fig. 2.—A fragility test in a case of moderately severe pneumonia. Hemolysis is visible above a concentration of 0.36 per cent, from which point it increases, reaching completion at 0.3 per cent.

From one to four days after the first appearance of lobar pneumonia the resistance of the red blood cells to hemolysis in hypotonic saline solution increases (fig. 2). In mild cases this depression of fragility may not go below 0.4 per cent, while in severe cases it may go as low as 0.32 or 0.3 per cent. The low point of beginning hemolysis persists until from one to three days after the febrile crisis, when a more or less abrupt return to normal occurs. In fatal cases the depression continues with increasing severity to the termination of the disease.

The whole scale of hemolysis is lowered as a unit; i. e., the point at which hemolysis is complete is lowered about the same degree as the point at which hemolysis begins. Therefore, only the latter, as it is easier to read, is considered here. Hence, on the charts fragility is shown as the point at which hemolysis begins and is determined by the first faint yellowish-red discoloration of the supernatant fluid.

CASE 1 (fig. 3).—S. C. C., a Brazilian man aged 38, entered the hospital on the fifth day of illness, demonstrating typical signs and symptoms of lobar pneumonia in the lower lobe of the left lung. He was at no time extremely ill, and after having a temperature between 38 and 39 C. (100.4 and 102.2 F.) for five days he improved abruptly on the sixth day in the hospital. From this point on his recovery was rapid and uneventful, and he was discharged thirteen days after admission.

This patient had a fragility curve typical of that associated with mild pneumonia. Beginning with figures which were normal or slightly above on the first three days, the curve dropped rather abruptly to 0.4 per cent, at which point it remained until three days after resumption of the normal temperature, when it rose to normal levels and remained there.

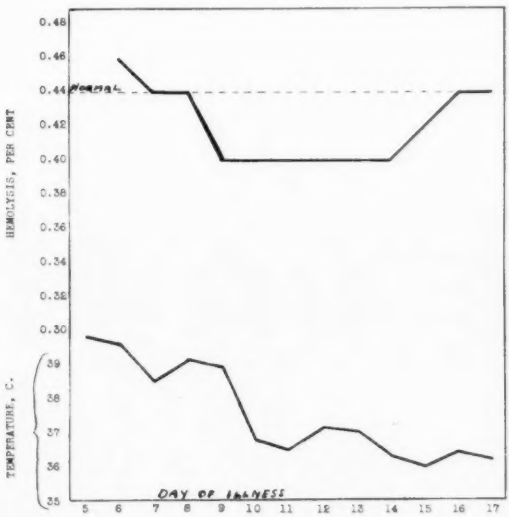

Fig. 3 (case 1).—A typical fragility curve in a case of mild pneumonia.

CASE 2 (fig. 4).—A. P. de S., a Brazilian man aged 25, entered the hospital on the fourth day of illness with typical signs and symptoms of lobar pneumonia in the lower and middle lobes of the right lung. The course was severe, and the patient for several days was extremely ill, as shown by the temperature chart. The fall in temperature was by lysis, but the recovery was fairly rapid, and the patient was discharged from the hospital thirteen days after admission.

This case illustrates the course of erythrocyte fragility in lobar pneumonia of moderate severity. Starting with subnormal figures on the second day in the hospital, the point of beginning hemolysis dropped steadily and rapidly to as low as 0.36 per cent on the eighth day of the illness. The recovery was not abrupt, as shown by the hesitancy with which both the temperature and the erythrocyte fragility returned to normal.

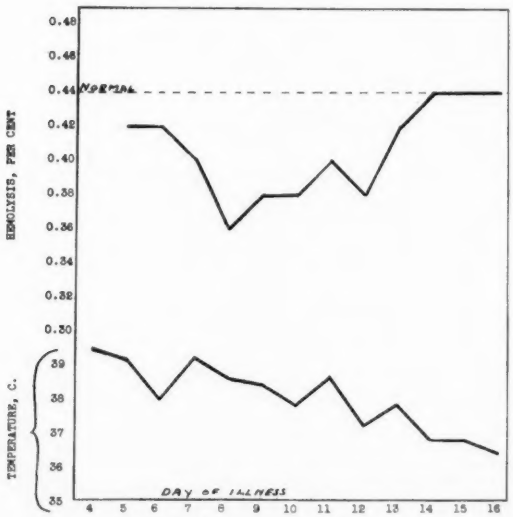

Fig. 4 (case 2).—Showing the course of erythrocyte fragility in a case of lobar pneumonia of moderate severity.

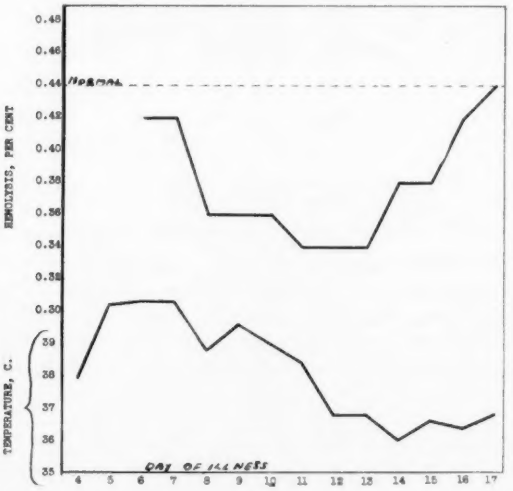

Fig. 5 (case 3).—The erythrocyte fragility curve in a case of pneumonia of extreme severity.

CASE 3 (fig. 5).—J. L. S., a Brazilian man aged 25 years, entered the hospital on the fourth day of his illness, presenting typical signs and symptoms of lobar pneumonia in the lower lobe of the left lung. He was extremely ill, and for several days little hope was held for his recovery. However, after seven days in the hospital his temperature dropped rather abruptly, and he was discharged as convalescent fourteen days after admission.

The clinical impression of extreme severity was substantiated by the erythrocyte fragility curve. Starting with a subnormal figure on the third day after the patient's admission to the hospital, the point of beginning fragility dropped in one day to 0.36 per cent, paused there for two days and then receded further to the alarming level of 0.34 per cent. The fragility continued at this very low point for three days before returning to normal.

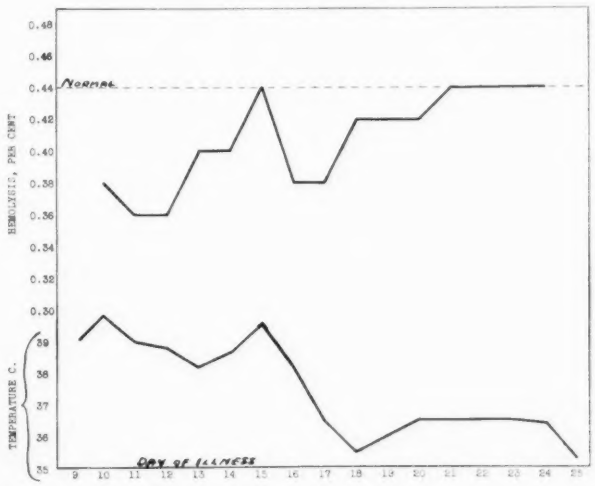

Fig. 6 (case 4).—Curves illustrating the erythrocyte fragility in a pneumonic process of a week's duration.

CASE 4 (fig. 6).—A. F. da S., a Brazilian man aged 39 years, entered the hospital on the ninth day of his illness with fully developed lobar pneumonia in the lower lobe of the left lung. His course was extremely severe, and after a temporary lowering of the temperature there were signs of a new involvement in the lower lobe of the right lung, which threatened to prove fatal. The patient rallied, however, and after seventeen days in the hospital was discharged as convalescent.

This case illustrates a primary low figure for erythrocyte fragility, doubtless because the pneumonic process was over a week old at the time of admission. After two days at 0.38 per cent, the hemolysis level rose, and three days later it was at 0.44 per cent, a normal figure. Then it dropped suddenly back to 0.38 per cent, which corresponded well with the clinical impression of new involvement in the lower lobe of the right lung. Following the remission in fever, the fragility figures returned to normal and remained there.

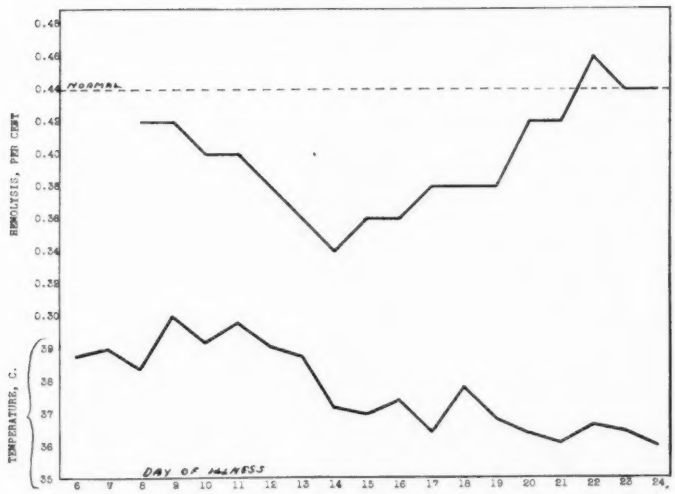

Fig. 7 (case 5).—Curves showing the uncertain course of the temperature and the fluctuation at the point of beginning hemolysis.

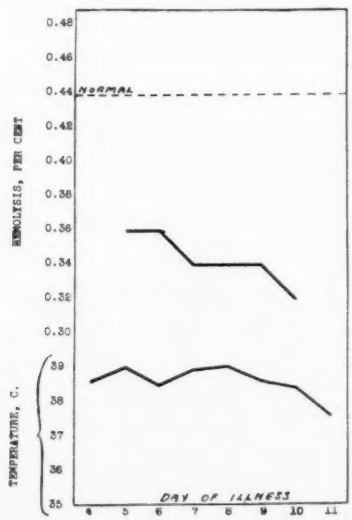

Fig. 8 (case 6).—Curves showing progressive depression of the erythrocyte fragility in a fatal case of lobar pneumonia.

CASE 5 (fig. 7).—B. C. de M., a Brazilian youth 19 years of age, entered the hospital on the sixth day of his illness. After four days of indeterminate signs and symptoms, on the fifth day he exhibited typical lobar pneumonia in the lower lobe of the left lung. The course was severe and long drawn out, with no abrupt crisis but with several slight recurrences after the initial fall in temperature. The involved area gradually cleared, and the patient was discharged as convalescent after eighteen days in the hospital.

Following the uncertain course of the temperature curve, the point of beginning hemolysis also fluctuated in this case. The low level reached on the eighth day in the hospital and the hesitancy exhibited in returning to normal are in perfect harmony with the signs and symptoms.

CASE 6 (fig. 8).—R. N. de L., a Brazilian man aged 37 years, entered the hospital on the fourth day of his illness with signs and symptoms of lobar pneumonia involving the entire left lung. Treatment was of no avail, and the patient died eleven days after admission. Autopsy showed massive consolidation of both lobes of the left lung, with fibrinopurulent pericarditis.

The first test for fragility of the erythrocytes, made on the second day the patient was in the hospital and on the fifth day of the disease, showed hemolysis beginning at 0.36 per cent. Succeeding daily examinations showed progressive depression of the fragility, and the day before death occurred a low point of 0.32 per cent was reached.

COMMENT

I have been unable to show any significant differences in pneumonia as seen in this latitude and that seen in more northern countries. The etiologic agent is the pneumococcus, and apparently any of the four recognized types may act as the infectious agent. Pathologic observations show massive lobar consolidation, such as one sees in pneumonia elsewhere. The sole difference is that owing to the previously debilitated state of many of the patients because of chronic disease and malnutrition pneumonia carries a high mortality rate.

The type of therapy has not seemed to play any part in the changes in fragility. In the first half of the cases studied no specific therapy was used and only supportive treatment was given, but in the latter half the patients were given optochin base. On the latter regimen they fared better. Therefore, as would be expected, when pneumonia is less severe fragility is not depressed to so great a degree.

It is difficult, of course, to say just when in the course of pneumonia the depression in fragility begins to occur. Many of the patients enter late, on the fourth or fifth day of their illness, or even later. These are found to have fragility rates as low as 0.38 or 0.36 per cent on admission. In the few cases which I have been fortunate enough to observe early it seems that the first appearance of decreased fragility, as well as the return to normal figures, lags from one to three days behind the changes in temperature. Thus a patient may enter the hospital with a high fever and maintain that high fever for two or three days before the point of beginning hemolysis begins to drop. Likewise, the depression in fragility may persist for two or three days after the febrile crisis.

I have made some study of the relation of other factors, such as the incidence of cultures of the blood giving positive results, the Arneth-Schilling counts, the toxic granulation of neutrophils and the total white blood cell counts, but I have been able to show only that with these special tests patients with severe pneumonia show more marked changes in fragility than those with a mild form of the disease. This relationship, however, needs more detailed study.

SUMMARY

Attention is called to the use of a determination of erythrocyte fragility in pneumonia. A modified technic for the carrying out of this test is explained, which gives accurate salt concentrations and uniform results. In pneumonia, depending on the severity of the illness and on its toxicity or the amount of lung tissue involved, the resistance of the red blood cells to hemolysis becomes greater. When the disease is mild, this may amount to as little as from 0.02 to 0.04 per cent, while when it is severe, it may be as great as 0.14 per cent. In fatal cases the resistance of the erythrocytes is very great, becoming progressively more marked as the disease advances.

There is a possible use for such an examination as an aid to prognosis. From the limited number of cases presented it may be stated that mild pneumonia causes only slight changes in fragility. Therefore, it may be assumed that as long as the erythrocyte resistance remains above 0.4 per cent the prognosis is good. However, I have seen patients recover in whom the point of beginning hemolysis had been as low as 0.34 per cent. The crisis in fragility lags from one to three days behind the crisis in fever, and it is not unusual to see low fragility readings from one to three days following the restoration of the normal temperature.

The mechanism is not clear. If it were directly dependent on toxicity or on the degree of bacteremia, one would expect the restoration to normal of the fragility of the red cells to be coincident with the cessation of fever. It seems more likely that it is a phenomenon intimately related to the amount of lung tissue consolidated and thus connected with the oxygen-carbon dioxide equilibrium of the blood. Further experimental work is needed to clear these points.

It is acknowledged that the cases reported here all occurred in Brazilians and that there may be some racial idiosyncrasy of which I am not aware. Also, as shown before,[1] most of the patients in this region are carriers of chronic malaria, many have syphilis and almost all have one or more types of intestinal parasites. In nearly all the spleen is enlarged from one to four times. The series of normal patients in which I have shown that the normal limits for erythrocyte fragility in this

area are the same as in more northern climates and in the white race, i. e., from 0.36 to 0.44 per cent, would tend to show that the same pathologic reactions would also be present. This is not conclusive and awaits the proof by application of the test in cases of pneumonia in the temperate zone.

Further research should point in two directions, viz., toward infections in general and toward pulmonary disease in particular. I should be greatly interested in the results of the test carried out in a series of cases of pulmonary tuberculosis and of congestive heart failure in which the pulmonary function is seriously impaired.

CONCLUSIONS

The fragility of the erythrocytes in pneumonia is discussed; cases are presented, and a modified technic is described. It is believed that the use of the test may open new avenues in the investigation of pneumonia, and it is suggested that the test be employed in cases of other infections, particularly of the pulmonary type. Acknowledgment is made that a difference in climate and race may cause some difference in results. A series of tests for fragility on normal inhabitants of this region is presented.

Dr. Colin Beaton and Dr. Siqueira Mendes granted me permission to use the cases presented, and Senhor Ivahy Ribeiro gave technical assistance.

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1935

FRANCIS M. RACKEMANN, M.D.
BOSTON

In January 1935 a review of the current literature on allergy was published in the ARCHIVES OF INTERNAL MEDICINE.[1] The present paper represents a continuation and extension of that work. During the year the number of new titles under the headings anaphylaxis, allergy, asthma, hay fever and eczema has been large, and, as before, a good deal of selection has been necessary and no doubt certain important articles have been missed.

An editorial[2] in *The Journal of the American Medical Association* for June 1, 1935, says: "Perhaps it is time now to examine the definition [of allergy] and determine its present status. . . . In the main it would probably be well to restrict the term to those disorders of sudden onset in which a specific tissue hypersensitivity is demonstrable." In last year's review it was pointed out that allergy is used to connote the mechanism of three different states, in each of which there is evidence of tissue sensitiveness. Hay fever and asthma are typical of the group characterized by reactions of the immediate urticarial type whenever the patient comes in contact with the allergen. Certain of the infectious diseases cause a tissue reaction of another kind, namely, an inflammation which appears not in a few minutes but in many hours after contact with the exciting agent. The reaction to tuberculin is the classic example, although one recognizes that its severity, its time relation, and, indeed, its character can be modified by changes in the infected animal as well as in the material and method used for its demonstration. Finally, in certain diseases of the skin there is evidence that the sensitiveness, the allergy, is of the skin alone and not of any other tissue. It is a "local allergy." If all this is true, it is inevitable that the conception of allergy, as previously stated, must apply to a wide variety of clinical states, and, regarded broadly, allergy appears to be intimately concerned

1. Rackemann, F. M.: Allergy: A Review of the Current Literature, Arch. Int. Med. **55**:141 (Jan.) 1935.

2. Definition of Allergic Diseases, Editorial, J. A. M. A. **104**:2000 (June 1) 1935.

with the whole immune process, with the resistance of the host to disease. To my mind this seems proper and wholesome, and I believe that a broad definition is wisest and safest at this time. It is necessary that those who are interested in hay fever, asthma and eczema, that is, in the immediate allergic reaction, should keep an eye on those other clinicians and the bacteriologists who are interested in the late inflammatory allergic reaction. There is definite evidence of a relation between the reactions, and one must understand the principles of both. On the other hand, the group of patients with hay fever, asthma or eczema is so typical and exhibits reactions which are so characteristic that it seems necessary to have a subgroup under the heading of allergy in which to place them. Coca has suggested "atopy," with "atopic" reactions elicited by "atopens," and has included in the definition the factor of heredity. The idea has advantages, even though it would probably be impossible so to define the subgroup that every condition would be placed either squarely in it or squarely out of it. The fact is that with the present knowledge it is impossible to dig beneath the mass of detail to see the fundamental principles under what is called clinical allergy and how far these principles will apply to disease as a whole.

What is the purpose and function of the reactions which are called "allergic"? This question cannot yet be answered, and it is easier to describe a number of possible functions which the reactions do not accomplish. The literature which deals with the relations of allergy and immunity is reviewed well by Lay Martin,[3] who points to an almost complete dissociation of the two conditions, as follows: First, animals once allergic and immune lose their allergy, that is, cutaneous sensitivity, with the passage of time, while retaining their immunity. Second, animals can be immunized without producing allergy at the same time. Third, there is proof that even though cutaneous sensitivity to bacterial proteins may develop in animals, immunity does not develop. Fourth, cutaneous sensitivity can be made to disappear without loss of immunity. Finally, immunity can be transferred passively to other animals without making them allergic, that is, without causing cutaneous sensitivity.

Whereas these statements are all true in a strict sense, a greater consideration of the time factor will modify some of them. For example, as described last year, Kahn has demonstrated that cutaneous sensitivity, abolished promptly by an intravenous dose of antigen, tends to return fairly rapidly after the treatment. Passive immunity is obviously a temporary state dependent primarily on humoral factors.

3. Martin, Lay: The Recent Trend Toward a Differentiation Between Allergy and Immunity, and the Relationship to Clinical Medicine, Ann. Int. Med. **8**:483, 1934.

On the other hand, there is increasing evidence that the tissues are the important element in immunity. If allergy is primarily a tissue function while immunity is primarily a humoral function, it is not surprising that the two may be separated under certain circumstances, whereas most of the time they work together.

Kahn lays further stress on tissue reactions in immunity. In two new papers [4] he describes experiments with what might be called double antigens. When diphtheria antitoxic horse serum is mixed with toxin and the mixture is then injected into a normal rabbit, nothing happens; but if it is injected into a rabbit sensitive to horse serum the animal dies because the sensitized tissue attracts and holds the antitoxic horse serum. When the toxin and the antitoxin are injected separately the amount needed to protect a rabbit sensitive to horse serum is definitely greater than the amount needed to protect a normal rabbit. Whether the tissue merely holds the antitoxin in some combination or whether a reaction occurs to destroy the antitoxin is uncertain.

Teale [5] also emphasizes the importance of tissue immunity. In studying the time required for the disappearance of bacteria after injection into the circulation, he noted that the time was about the same in immune animals as it was in normal animals and that the presence or absence of immunity depended not on the primary clearance of bacteria from the blood stream but on a later recurrence of the bacteremia. Experiment showed that in the immune animal a return of bacteremia does not occur even if at that time its blood has no power to protect other animals against the same organism. There is, then, ample evidence to indicate the importance of the tissues, and the interesting point is that tissue reactions can take place regardless of whether or not the blood serum of the animal shows evidence of humoral immunity.

Further light on the development of sensitization comes from the paper by Schultz and Swift.[6] By treating rabbits with repeated intradermal injections of streptococci to produce a low grade cutaneous infection, the authors observed that when the same animals were then sen-

4. Kahn, Reuben L., and McDermott, E. B.: Studies on Tissue Reactions in Immunity: XV. Union Between Specific Antigen and Skin of Protein-Immunized Rabbits, J. Immunol. **27**:125, 1934. Kahn, Reuben L.: Studies on Tissue Reactions in Immunity: XVI. Capacity of Different Tissues of Protein-Immunized Rabbits to Combine with Antigen, ibid. **27**:143, 1934.

5. Teale, F. H.: Some Observations on the Relative Importance of the Reticulo-Endothelial Tissues and the Circulating Antibody in Immunity: I. Bacterial Immunity in Relation to the Rôle Played by the Circulating Antibody and the Tissues Following Intravenous Introduction of the Bacteria, J. Immunol. **28**: 133, 1935.

6. Schultz, M. P., and Swift, H. F.: The Effect of Antecedent Infection and Immunization with Streptococci upon the Reactivity of Rabbits to Horse Serum, J. Exper. Med. **60**:323, 1934.

sitized to horse serum the reactions to subsequent doses of horse serum were much more violent than normal. As an explanation of this observation they suggest that the previous treatment with streptococci caused a stimulation of the reticulo-endothelial system and thus acted to improve the antibody-producing mechanism. The previous treatment of the animal had led to a nonspecific change in the response of its antibodies. The thought is interesting in connection with many so-called anamnestic reactions.

In the meantime, Kline and Young,[7] working in M. B. Cohen's clinic, discuss the differences between what they call reversible and irreversible allergic inflammation. They describe the pathologic process which is characteristic of many allergic states. This process consists of edema, with accompanying mononuclear and eosinophilic infiltration, and is seen typically in patients with asthma. This type of inflammation is capable of disappearing without trace. Whether the pathologic process of allergy is a characteristic of a particular agent or of the resistance of the host is an interesting question, hard to answer. An irreversible allergic inflammation is seen in such destructive reactions as the Arthus phenomenon.

CHEMISTRY OF HYPERSENSITIVENESS

The chemical nature of the active substance in pollen extracts is still a controversial problem. The standardization of extracts was formerly on the simple but insecure basis of their total nitrogen content. In 1932 Cooke and Stull[8] suggested that the protein nitrogen, the factor precipitable by phosphotungstic acid, is a more accurate index of the strength of the solution and that the active principle is a protein.

Coca,[9] however, took issue with Cooke and Stull: "In a number of consistent experiments, we have seen such a rapid dialysis of phosphotungstic acid-precipitable nitrogen as to make it certain that by far the greatest part of it is not native protein." Furthermore, the contents of the bag after dialysis, while being so low in nitrogen content, retained its skin test activity, the dialysate being quite inert.

In the meantime, Loeb in 1929[10] and 1930[11] demonstrated that the active principle can be inactivated by tryptic digestion and dialysis

7. Kline, B. S., and Young, A. M.: Normergic and Allergic Inflammation: Cases of Reversible and Irreversible Allergic Inflammation, J. Allergy **6**:247, 1935.

8. Cooke, R. A., and Stull, A.: The Preparation and Standardization of Pollen Extracts for the Treatment of Hay Fever, J. Allergy **4**:87, 1933.

9. Coca, A. F.: On the Plan of Standardization of Pollen Extracts Proposed by Cooke and Stull, J. Allergy **4**:354, 1933.

10. Loeb, L. F.: Ueber die chemische Natur der Allergene: III. Pollen von Alopecurus (Fuchschwanz Gras), Klin. Wchnschr. **8**:926, 1929.

11. Loeb, L. F.: Untersuchungen über die chemische Natur des Allergene, Biochem. Ztschr. **220**:432, 1930.

and further that it can be precipitated by alcohol. Loeb also concluded that it either is a protein or is closely bound to a protein. In the same year Black [12] noted that the alcoholic precipitate when purified by reprecipitation gave evidences of a carbohydrate and incidentally was skin test-active in a dilution of 1 : 240,000. In 1932 Gough [13] demonstrated the presence of a carbohydrate in timothy pollen.

It is apparent that the methods and technic involved in this study are of paramount importance. Dialysis is always uncertain, since it depends so much on the membrane used and the time allowed. Indeed, Unger, Cromwell and Moore [14] observed that skin test-active substances are often dialyzable, and in a direct study they could observe no correlation between the response of the sensitive animal and the dialyzable material. Both the dialyzable and the nondialyzable fractions caused a reaction.

These previous studies are reviewed here because another method of analysis has been developed recently. A year ago Spain and Newell [15] devised an apparatus for forcing solution through semipermeable membranes under pressure. The membranes used were no. 300 and no. 1200 cellophane. Such an ultrafilter holds back the colloidal particles, the protein. It was observed that the filtrate was inactive, whereas the colloidal residue retained almost all the original activity. The filtrate contained the nonprotein nitrogen, and since it gave a positive reaction to the Molisch test, there is evidence that it contained carbohydrate. On the other hand, the nitrogen precipitable by phosphotungstic acid was not held back completely, and so it must be concluded that the degree of activity is not exactly parallel to that of the precipitable nitrogen.

Meantime, Osgood and Hubbard [16] passed an extract of timothy pollen through several different Seitz filters and observed that the total nitrogen, the nitrogen precipitable by phosphotungstic acid and the nitrogen precipitable by tri-chloracetic acid were all reduced but that the nitrogen in the fraction precipitable by tri-chloracetic acid was reduced most of all and that the amount of reduction of this particular nitrogen fraction corresponded closely to the amount of reduction in skin test activity.

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12. Black, J. H.: A Soluble Specific Carbohydrate of Ragweed, J. Allergy **2**: 161, 1931.

13. Gough, G.: A Polysaccharide from the Pollen of Timothy Grass, Biochem. J. **26**:1291, 1932.

14. Unger, L.; Cromwell, H., and Moore, M.: Studies on Pollen and Pollen Extracts: VIII. Dialyzability of Pollen Allergens, J. Allergy **3**:253, 1932.

15. Spain, W. C., and Newell, J. M.: The Ultrafiltration of Ragweed Pollen Extracts, J. Allergy **5**:455, 1934.

16. Osgood, Howard, and Hubbard, R. S.: The Skin Exciting Activity of a Timothy Pollen Extract As Measured by Its Content of Three Nitrogen Fractions, J. Allergy **6**:349, 1935.

Benjamins, van Dishoeck and German,[17] however, state: "When pollen extract is filtered through a protein-tight celloidin membrane by means of pressure, positive skin reactions can be obtained with the filtrate in all hay fever subjects." The active substance passing the filter has a small molecular weight. This article of Benjamins and his associates, however, contains a more important point. If pollen extract was mixed with a colloid (serum is effective, but a variety of other colloids, like egg albumin and gelatin, are equally effective; so the mixture is not an anaphylatoxin), the mixtures caused a strongly positive cutaneous reaction in patients who were insensitive to the pollen extract alone or to the adjuvant alone in the dilutions used. Other substances too could activate pollens, certain amino-acids occasionally. Tapioca was particularly effective, but other polysaccharides, like starch, inulin and glycogen, had no effect, and dextrin, dextrose and other pure sugars had no effect. If the combination of ultrafiltrate and colloid was again filtered there was a great loss of activity in the filtrate, and when the process was repeated a third time with stronger colloid (gelatin) all activity was removed by the filter. The results of these experiments suggest that the active principle of pollen extract is in a small molecule which needs a larger complex for its activation.

The work of Caulfeild[18] has further complicated the question. Working with various chemical fractions of ragweed pollen on a series of cutaneous sites passively sensitized, he observed that desensitization readily followed persistent treatment of the particular site but that desensitization with a fraction did not necessarily leave the site desensitized to the whole extract. He concluded that the skin test-active substance in ragweed is not single but multiple and that the reagins are likewise multiple. This observation offers another explanation of so many discordant results.

Investigations into the production of artificial sensitization to compounds of simple chemical structure have been continued. Bernstein[19] sensitized guinea-pigs to the pollen of Iva xanthifolia (bur-weed; marsh-elder) by a simple technic. He mixed equal volumes of 4 per cent pollen extract and horse serum and let the mixture stand for several days. Guinea-pigs were sensitized by three intradermal injections, each

17. Benjamins, C. E.; van Dishoeck, H. A. E., and German, J. L. M.: Studies on the Active Substance of Grass Pollen: I. Activation of a Small Molecular Weight Active Group Through Colloidal Substances, J. Allergy **6**:335, 1935.

18. Caulfeild, A. H. W.: Prausnitz-Küstner Reaction with Sera of Ragweed Hay Fever Patients to Ragweed Carbohydrate Fractions, Proc. Soc. Exper. Biol. & Med. **31**:573, 1934.

19. Bernstein, C., Jr.: Studies on Anaphylaxis with Pollen, J. Exper. Med. **61**: 149, 1935.

of 0.4 cc. at four day intervals. Later when 0.4 cc. of the pollen extract was injected intravenously, shock occurred. This is similar to the work of Horsfall,[20] who observed that mixtures of formaldehyde and serum, both native and foreign, will immunize rabbits so that precipitins are formed for homologous and heterologous serums treated with formaldehyde, and at the same time a markedly increased cutaneous sensitiveness develops to formaldehyde alone. Cutaneous tests are made with dilutions from 1 : 200 to 1 : 500,000. Later, Horsfall [21] studied a patient sensitive to solution of formaldehyde U.S.P. and observed that any exposure, whether by injection, immersion or (and this is especially interesting) inhalation, produced the characteristic cutaneous manifestations. The hypersensitiveness was strictly specific to formaldehyde: Acetaldehyde, paraldehyde and other aldehydes caused no reaction. Benzaldehyde did cause a reaction, but it was irritating to controls as well. Passive transfer was not accomplished. An interesting observation was the difference in time between reactions to uncombined formaldehyde, which were delayed, and reactions to protein treated with formaldehyde, which were immediate. This suggests that the reaction depends on the formation of a substance resulting from the union of formaldehyde with a protein or with a constituent of the skin of the hypersensitive person.

The whole field of sensitization with simple chemical compounds is reviewed by Landsteiner and Jacobs,[22] who report a series of successful experiments in the sensitization of guinea-pigs to a variety of aromatic compounds. These studies, conducted by Spain, Benjamins, Horsfall and Landsteiner, dwell on the theme that specific activity is a function of a small nucleus attached to a larger body having protein characteristics. The picture is familiar in connection with haptens as well as in connection with the carbohydrate complex, which confers species specificity on the protein of the pneumococcus.

Meantime, Ratner and Gruehl [23] sensitized animals to whole milk and observed that shock could be caused by the injection of casein, lactalbumin and lactoglobulin, as well as of a number of treated milks said to be allergen-free. The reduction of antigenic potency by heat depends merely on a partial coagulation which delays absorption by the

20. Horsfall, Frank L., Jr.: Formaldehyde and Serum Proteins, J. Immunol. **27**:553, 1934.

21. Horsfall, Frank L., Jr.: Formaldehyde Hypersensitiveness: An Experimental Study, J. Immunol. **27**:569, 1934.

22. Landsteiner, K., and Jacobs, John: Studies on the Sensitization of Animals with Simple Chemical Compounds, J. Exper. Med. **61**:643, 1935.

23. Ratner, Bret, and Gruehl, H. L.: Anaphylactogenic Properties of Milk: Immunochemistry of the Purified Proteins and Antigenic Changes Resulting from Heat and Acidification, Am. J. Dis. Child. **49**:287 (Feb.) 1935.

digestive tract. In another paper [24] Ratner and Gruehl indicate that so-called allergy to carbohydrate foods depends on the small residue of protein which the foods contain and that malt extracts contain hordein and are antigenic while corn syrups and other sugars are non-anaphylactogenic. In a third and very useful article Ratner [25] presents the practical aspects of the treatment of milk allergy.

In considering chemistry the observations of Cohen [26] on the nature of the house dust allergen must be included. Cohen demonstrated that extracts of new and fresh cotton linters cause a reaction very infrequently on the skin of patients sensitive to house dust but that extracts of other cotton which is old and used causes a strong reaction. In my own laboratory, the findings in the study of kapok were the same; there is a marked difference in the reactions caused by new and those caused by old kapok. These results will be described in a paper by Wagner and Rackemann now in press.

IMMUNOLOGY OF HYPERSENSITIVENESS

The biologic relationship between substances of similar character is of great practical importance in the clinical management of allergic patients with allergic manifestations. There are two methods of studying their relationship.

In 1925 Coca and Grove [27] made a study of the atopic reagins and observed that these antibodies could be neutralized. When hypersensitive serum containing reagins from a patient with asthma or hay fever was injected into normal cutaneous sites on the arm of normal recipients, the sites became sensitive to the same substances to which the patient was sensitive. Coca and Grove observed that if these passively sensitized sites were treated repeatedly with the corresponding allergens injected into the same areas the reactions, which were extensive at first, tended to become smaller later and finally to disappear; the sites were desensitized, but they would show a reaction again when tested further with some other allergen. Evidently the desensitization was a highly specific phenomenon. In the same article Coca and Grove describe a second method. When a mixture of atopic serum (containing reagins to horse dander) and of atopen (the extract of horse dander) was injected into a normal recipient the reagins in the mixture were neutralized, as shown by the fact that a test of the site twenty-four hours later

24. Ratner, Bret, and Gruehl, H. L.: Anaphylactogenic Properties of Malted Sugars and Corn Syrup, Am. J. Dis. Child. **49**:307 (Feb.) 1935.

25. Ratner, Bret: The Treatment of Milk Allergy and Its Basic Principles, J. A. M. A. **105**:934 (Sept. 21) 1935.

26. Cohen, Milton B.: Observations on the Nature of the House Dust Allergens, J. Allergy **6**:517, 1935.

27. Coca, A. F., and Grove, Ella F.: Studies in Hypersensitiveness: XIII. A Study of the Atopic Reagins, J. Immunol. **10**:445, 1925.

with an extract of horse dander resulted negatively. This second experiment has been repeated by Walzer and Bowman [28] and by Cooke and his associates,[29] and the general principles are confirmed.

These two methods have provided a means of distinguishing between closely related substances in their biologic activity. For example, the horse dander-horse serum relationship has been studied by Tuft,[30] who observed that passively sensitized sites desensitized with horse dander are also desensitized to horse serum, but, on the other hand, horse serum is not capable of desensitizing the sites to horse dander. As Tuft concludes, there is an additional factor in the dander which is not present in the serum. Using the method of desensitization of passively sensitized sites, Simon [31] noted that the serum of patients sensitive to horse serum could sensitize the sites in a normal recipient not only to horse serum but to that of a wide variety of other animals. When later a series of sites were desensitized with guinea-pig serum and then tested with the serums of other animals the reactions were entirely negative. Evidently there is a species-nonspecific factor present in all mammalian serums. The specificity of different species of the Caddis fly has been studied by Osgood [32] with similar methods.

Harley [33] has made a study of reagin-allergen mixtures. He observed that they may produce reactions in normal skin. When the allergen is bound by the reagin in vitro it can be freed by heating to 56 C. or enough to destroy the reagin; the union is influenced markedly by time and temperature. To me it seems wiser and safer to use the method by which passively sensitized sites are desensitized with one substance and then tested with another.

Harkavy and Witebsky [34] call attention to the fact that whereas a single serum may contain reagins for a variety of substances, the con-

28. Walzer, M., and Bowman, K.: A Test Tube Neutralization Method for Studying the Identity and Properties of Reagins, J. Allergy **1**:464, 1930.

29. Stull, A.: Cooke, R. A., and Barnard, J. H.: The Biologic Identity of Certain Grass Pollens Causing Hay Fever, J. Allergy **3**:352, 1932. Cooke, R. A.; Stull, A.; Hebald, S., and Barnard, J. H.: Clinical and Serologic Study of the Relationship of Giant (Ambrosia Trifida) and Low (Ambrosia Artemisiaefolia) Ragweed Pollen, J. Allergy **6**:311, 1935.

30. Tuft, L.: Further Studies in Serum Allergy: VI. Antigenic Relationship Between Horse Dander and Horse Serum Sensitivity, J. Allergy **6**:25, 1934.

31. Simon, Frank A.: Species Non-Specific Antigenic Factor in Mammalian Serum, J. Allergy **6**:1, 1934.

32. Osgood, Howard: Comparison of Reagins to Separate Species of Caddis Fly, J. Allergy **5**:367, 1934.

33. Harley, D.: Study of Reagin-Allergen Mixtures, Brit. J. Exper. Path. **14**: 171, 1933.

34. Harkavy, J., and Witebsky, E.: Studies on Specificity in Multiple Hypersensitiveness by Quantitative Titration and Absorption of Reagins, J. Allergy **6**: 437, 1935.

centration of these reagins may vary to some extent and that in studying reagins it is necessary to consider the dilutions of the serum as well as the dilutions of the allergic substance.

On a somewhat related topic is the paper by Stevens,[35] in which he describes his effort to demonstrate the presence of reagins by chemical means, using those methods which are often successful in demonstrating the combination of agglutinins with bacteria. His results were negative.

HOST FACTOR IN ALLERGY

The host factor in allergy has received scant attention of late. Bray [36] discusses the importance of endocrine dysplasias in patients with asthma and hay fever and quotes figures of others to indicate that these disturbances are rare in patients with allergy, just as allergy is a rare complication in patients with frank endocrine disorders. This subject, however, may be more important than it now appears, because in the last analysis there must be some fundamental reason for the fact that certain persons have hay fever and others do not and that tissue reactions of the immediate type are predominant in one case and not in another.

Hara [37] studied hay fever among the Japanese population of Los Angeles and found that the incidence was about 3.5 per cent of the Japanese population in that part of southern California. Evidently the yellow races have no racial immunity.

The complement content of the blood is smaller in persons with allergic disease than in normal persons, as determined by Paul and Pely.[38]

Studies on the relation of the adrenal glands to allergic phenomena have been carried out by Cohen, Rudolph and their associates.[39] Using the quantitative method previously described by Stewart and Rogoff, they sensitized dogs to horse serum and then studied the amount of epinephrine in the blood during the subsequent shock. No significant alteration in the rate of secretion of epinephrine could be demonstrated.

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35. Stevens, F. M.: Chemical Study of the Pollen-Sensitizing Antibody Combination, J. Immunol. **29**:273, 1935.

36. Bray, G. W.: Recent Advances in the Treatment of Asthma and Hay Fever, Practitioner **133**:368, 1934.

37. Hara, H. J.: Hay Fever Among Japanese: I. Arch Otolaryng. **20**:668 (Nov.) 1934.

38. Paul B., and Pely, M.: Decrease of Complement Content of Blood in Allergic Disease, Klin. Wchnschr. **14**:163, 1935.

39. Cohen, M. B.; Rudolph, J. A.; Wasserman, P., and Rogoff, J. M.: The Output of Epinephrine from the Adrenal Glands During Anaphylactic Shock, Am. J. Physiol. **106**:414, 1933.

Cohen and Rudolph [40] experimented on man by giving large doses of strychnine, in the hope that this would stimulate the secretion of epinephrine. Doses up to 1/6 grain (0.01 Gm.) were injected intramuscularly, producing hypertonicity in most of the patients. The asthma was partially relieved, but the good effect was overshadowed by the complicating hypertonicity, and consequently the method can have no general use.

In another series of studies Cohen and Rudolph [41] investigated the possible therapeutic effect of extract of the adrenal cortex. A material called "interrenalin," made by Dr. Rogoff and found potent in patients with Addison's disease, was administered for several weeks to 4 patients with severe asthma. No effect, however, was observed. On the other hand, Wolfram and Swemer [42] studied the effect of extract of the adrenal cortex in protecting guinea-pigs against anaphylactic shock and noted that the majority of animals survived if the extract was administered from two to six hours before the test dose.

None of these studies are critical, but they indicate that there is no evidence that hay fever and asthma depend on a definite alteration in the endocrine, and particularly in the adrenal, function of the patient.

DIAGNOSIS

Discrepancy Between Cutaneous Reactions and Symptoms.—This has received further attention, and little by little students of allergy begin to realize that skin tests are far from giving the answer to every problem. This point was made last year, but repetition can do no harm.

Colmes, Guild and Rackemann [43] made cutaneous tests on the employees of a large bakery. Of 32 men, 15 gave a positive reaction to one or other allergen, but of these only 1 had symptoms which could be attributed to sensitiveness to wheat. For cutaneous sensitivity to develop is common, but for clinical sensitiveness to develop some additional factor, some "activator," is required.

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40. Cohen, M. B., and Rudolph, J. A.: Studies on the Relation of the Adrenal Glands to Allergic Phenomena: II. The Therapeutic Effect of Strychnine Stimulation of the Adrenal Medulla in Asthma, J. Allergy **6**:404, 1935.

41. Cohen, M. B., and Rudolph, J. A.: Studies on the Relation of the Adrenal Glands to Allergic Phenomona: III. On the Specific Therapeutic Effects of Cortical Adrenal Extract in Asthma, J. Allergy **6**:279, 1935.

42. Wolfram, J., and Swemer, R. L.: Cortin Protection Against Anaphylactic Shock in Guinea Pigs, J. Exper. Med. **61**:9, 1935.

43. Colmes, A.; Guild, B. T., and Rackemann, F. M.: Studies in Sensitization: The Influence of Occupation on Human Sensitization as Determined in a Study of Thirty-Two Bakers, J. Allergy **6**:539, 1935.

At the end of 1934, Rowe [44] submitted an evaluation of cutaneous reactions in patients sensitive to food and demonstrated, first, that the method of making cutaneous tests is of great importance and, second, that the substance used for the test is also of great importance, that two extracts bearing the same label often give widely different results. His observations show that in certain cases a positive reaction has no clinical significance, while in other cases the patient might be truly sensitive and yet fail to give a cutaneous reaction. Other observers have come to a similar conclusion from their clinical experience.

Colmes,[45] for example, observed that in 250 patients with asthma the cutaneous reactions were clinically important in only 40 per cent. He studied 222 patients with perennial vasomotor rhinitis and observed that the reactions were of importance in 25 per cent. He followed 93 patients with urticaria and noted that the reactions were significant in only 4 per cent. In patients with hay fever, however, the results were satisfactory, for in practically every instance the reactions and the symptoms seemed to go together.

Part of this discrepancy depends, of course, on the fact that the cutaneous reaction persists long after clinical sensitiveness has disappeared. Thus, Spink and Augustine [46] observed that extracts of Trichinella which produce immediate reactions in patients with trichinosis cause an immediate positive cutaneous reaction long after the disease has subsided. The reaction for precipitin likewise persists for a time after symptoms have cleared, but it does not last so long as the cutaneous sensitivity.

The Leukopenic Index.—Vaughan [47] has continued his studies, observing that a fall of the total number of leukocytes during digestion of a food to which the patient is sensitive corresponds to the symptoms in 81 per cent of the cases. It is his experience that cutaneous reactions correspond in only 64 per cent of the cases. Vaughan noted that the best time to demonstrate the fall in the leukocyte count is from thirty to ninety minutes after ingestion of the food. Mathematically the index is an expression of the amount of decrease in terms of the initial leukocyte count. Rinkel [48] has confirmed Vaughan's observations,

44. Rowe, Albert, H.: An Evaluation of Skin Reactions in Food Sensitive Patients, J. Allergy **5**:135, 1934.

45. Colmes, A.: A Clinical Evaluation of the Positive Skin Reaction in Asthma, Urticaria, Vasomotor Rhinitis and Seasonal Hay Fever, New England J. Med. **212**:725, 1935.

46. Spink, W. W., and Augustine, D. L.: The Diagnosis of Trichinosis with Especial Reference to Skin and Precipitin Tests, J. A. M. A. **104**:1801 (May 18) 1935.

47. Vaughan, W. T.: Further Studies on Leukopenic Index in Food Allergy, J. Allergy **6**:78, 1934.

48. Rinkel, H. J.: The Leucopenic Index in Allergic Diseases, read before the Association for the Study of Allergy, June 1935.

stating that the index is an important diagnostic aid, especially in the detection of sensitivity to a food. In Rinkel's experience one count forty minutes after the ingestion of food is satisfactory in 80 per cent of the cases.

Eosinophilia.—This is always a striking characteristic of allergy, being present in all the different manifestations. A rapid method for its determination is described by Friedman,[49] who recommends the use of a white blood cell pipet for making the count but with a diluting fluid containing 5 per cent each of an aqueous solution of eosin and of acetone in 100 cc. of water to be substituted for the usual dilute acetic acid. With this staining fluid the eosinophil cells are easily detected, and the other leukocytes can be seen at the same time. I have tried this method and can say that it is good.

Spangler [50] studied the eosinophil count in persons with syphilis and points out that the number of persons showing eosinophilia is greater if a larger number of counts is made. Evidently the proportion of eosinophils varies from time to time and within fairly wide limits.

The importance of eosinophils in the sputum of patients with asthma is emphasized by Knott and Pearson,[51] who state that the number of eosinophils tends to decrease as secondary infections appear. This subject needs further study, because personal experience indicates that high figures for the eosinophil count in the blood are often noted in cases of a chronic severe type of asthma, including those in which a search for possible causes in foods and dusts is mostly without result. In 1 or 2 cases it has seemed as though the height of the eosinophil count occurred when the severity of the asthma was greatest. That eosinophilia may persist for several years after recovery is the point of a paper by Theiler, Augustine and Spink,[52] who followed 7 cases of trichinosis for more than five years after the attack and observed that in 3 there was still eosinophilia of over 5 per cent.

The Clinical History.—This remains the one most important factor in the diagnosis of the exciting cause of asthma. This fact was emphasized in the review of last year, and it deserves emphasis again.

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49. Friedman, Townsend B.: A Rapid Method for the Determination of Blood Eosinophilia, J. A. M. A. **103**:1618 (Nov. 24) 1934.

50. Spangler, R. H.: Eosinophilia in Syphilis, J. Lab. & Clin. Med. **20**:733, 1935.

51. Knott, F. A., and Pearson, R. S. B.: Eosinophilia in Allergic Conditions, Guy's Hosp. Rep. **85**:94, 1935.

52. Theiler, H.; Augustine, D. L., and Spink, W. W.: On the Persistence of Eosinophilia and on Immune Reactions in Human Trichinosis Several Years After Recovery, Parasitology **27**:345, 1935.

CLINICAL MANIFESTATIONS

Hay Fever.—Pollen in the Atmosphere: Studies of atmospheric pollen have been continued. Durham [53] describes a gyrating instrument which can be rotated with a handle so as to draw in a large volume of air and collect on a glass slide the pollen which it contains. Nineteen hundred revolutions are equivalent to a twenty-four exposure, so that the machine makes it possible to test the concentration of pollen at any point in a few minutes. With this machine and by other methods Durham has gathered useful data, presented in two papers,[54] on the pollen in various areas in North America.

Vaughan and Crockett [55] discuss the importance of goldenrod and in another paper with Graham [56] compare the different surveys of pollen in Virginia which have been made in the last six years.

Sellers [57] describes the relative importance of grasses, weeds and trees in Texas.

Surveys of the concentration of pollen are coming in from foreign countries. From Scandinavia comes a survey by Baagøe,[58] and from Havana, one by Alvarez.[59] From Australia, Sharwood [60] describes the pollen content of the Melbourne air during the hay fever season from August 1933 to March 1934. From Hungary comes the report by Hlaváček and Blattný.[61]

Molds in the air as a source of hay fever and asthma are receiving more attention. Prince, Selle and Morrow [62] describe the cultures obtained by exposing Sabouraud plates to the air under different cir-

53. Durham, O. C.: A Simple Apparatus for Determining the Pollen Content of the Air, Aerologist **11**:10, 1935.

54. Durham, O. C.: The Pollen Content of the Air in North America, J. Allergy **6**:128, 1935; Pollen Studies in Selected Areas, J. A. M. A. **104**:1486, (April 27) 1935.

55. Vaughan, Warren T., and Crockett, R. W.: An Assay of Goldenrod as a Cause of Hay Fever, Ann. Int. Med. **6**:789, 1932.

56. Vaughan, Warren, T.; Graham, W. R., and Crockett, R. W.: Hay Fever Pollen Prevalences in Virginia: Review of a Six Year Survey, Virginia M. Monthly **60**:158 (June) 1933.

57. Sellers, Erle D.: Pollinosis in the Southwest, South. M. J. **28**:710, 1935.

58. Baagøe, K.: Pollen Content of Air in Hay Fever Season, Ugesk. f. læger **96**:570, 1934.

59. Alvarez, J. Cadrecha: Pollen in Air of Havana, Rev. med. cubana **45**: 651, 1934.

60. Sharwood, Marjorie M.: The Pollen Content of the Melbourne Air During the Hay Fever Season of August 1933 to March 1934, M. J. Australia **1**:326 (March 16) 1935.

61. Hlaváček, V., and Blattný, C.: The Quantity of Pollen in Atmosphere of Prague and Its Relation to Atmospheric Changes, Casop lék. česk **73**:1021, 1934.

62. Prince, H. E.; Selle, W. A., and Morrow, M. B.: Mold in Etiology of Asthma and Hay Fever, Texas State J. Med. **30**:340, 1934.

cumstances and the check of the results on their patients by testing them with extracts of corresponding molds. Of 18 patients tested, 11 showed positive cutaneous reactions to mold, and in 7 of the 11 the treatment "is encouraging."

The subject of molds as a whole is reviewed in an excellent article by Feinberg,[63] who includes a good bibliography. Positive reactions to molds and yeasts were obtained in 47 of 123 patients with hay fever and asthma, and, more important, it was possible to demonstrate that in many cases these molds were the actual cause of the difficulty.

A helpful botanic review of the fungi is that by Downing and Cousins,[64] who describe the exhibit of fungi at the meeting of the Massachusetts Medical Society. The generic relationship of the thallus plants, including algae and fungi, the mosses, the ferns and the seed plants, are described simply and clearly.

The specific treatment of hay fever is receiving rather less attention so far as the technical details are concerned. Cooke and his co-workers [65] describe the results of transfusion of blood to new patients, using the blood from other patients who appeared to be doing well. As much as 500 cc. of blood was given at a time, and the results were satisfactory in 80 per cent of the cases. Another series of patients received subcutaneous doses of 10 cc. each of blood from successfully treated patients, and again the results were fairly good, with a satisfactory outcome in 60 per cent of the cases. The interesting part of this study was the comparison of the serum reagins, for no material difference in the sensitizing capacity of the patient's blood was noted before or after the treatment by transfusion. From this Cooke concludes that the protection afforded by transfusion does not depend on the overproduction of antibodies. In another part of the work, the same authors report that although ragweed pollen extract can neutralize in vivo the reagins in the serum of sensitive but untreated patients, it does not neutralize the reagins in the serum of patients who have been treated successfully with it. After treatment, the serum-ragweed mixture is quite capable of passively sensitizing the cutaneous sites in normal persons. The authors conclude that successful treatment results in the development of an immune body which prevents the union of antigen and antibody.

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63. Feinberg, Samuel M.: Mold Allergy: Its Importance in Asthma and Hay Fever, Wisconsin M. J. **34**:254, 1935.

64. Downing, J. G., and Cousins, S. M.: Exhibit of Fungi Pathogenic to Man Shown at the One Hundred and Fifty-Third Anniversary of the Massachusetts Medical Society, New England J. Med. **211**:963, 1934.

65. Cooke, R. A.; Barnard, J. H.; Hebald, S., and Stull, A.: The Mechanism of Protection Produced by Injection of Pollen Extract in Hay Fever Patients, J. Allergy **6**:593, 1935.

Last year the report of Lichtenstein [66] on intravenous pollen therapy was described. No one has reported on the use of the method since.

Brown [67] continues to treat his patients with maximum doses of pollen extracts, reaching in many cases a dose of 1 cc. of a 1:10 dilution, which represents a content of from 100,000 to 200,000 units. With this treatment the cutaneous reaction disappears almost entirely, and all of his patients have done well.

Permanent results following the treatment for late hay fever are reported by Vander Veer and Clarke [68] in a group of 159 patients: Twenty per cent were cured; 33 per cent were greatly improved; 13 per cent were decidedly improved, and in 34 per cent this condition was as bad as ever as soon as the annual or perennial treatment was stopped.

Obviously, the problem of hay fever is not solved.

Asthma.—"De asthmate antiquo" is the title of a short paper by Baumann,[69] in which he reviews the history of asthma in antiquity. The Greeks had three classifications of difficult breathing: dyspnea, asthma and orthopnea. The article is worth reading.

The pathology of the vessels of the pulmonary circulation is well described in an important study by Brenner,[70] of Queen's Hospital, Birmingham, England.

Bubert and Warner,[71] as well as Michael and Rowe,[72] described the pathologic changes in patients who died of asthma.

Cutler and Wood [73] have developed a new method for producing experimental endobronchial occlusion. The injection of a 25 per cent aqueous solution of acriflavine hydrochloride will produce aseptic necrosis of the mucosa, which leads later to proliferation and fibrosis. Collapse occurs only in case all the bronchi to a certain lobe are occluded. The occurrence of collapse in patients with asthma has been

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66. Lichtenstein, M. R.: Intravenous Pollen Therapy, J. Allergy **5**:230, 1934.

67. Brown, G. T.: Further Experiences with Maximum Dosage Pollen Therapy, J. Allergy **6**:86, 1934.

68. Vander Veer, A., and Clarke, J. A., Jr.: Permanent Results Following Treatment for Late Hay Fever, J. Allergy **6**:551, 1935.

69. Baumann, E. D.: De asthmate antiquo, Janus **38**:139, 1934.

70. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation: I. Arch. Int. Med. **56**:211 (Aug.) 1935; II. **56**:457 (Sept.) 1935; III. **56**:724 (Oct.) 1935; IV. **56**:976 (Nov.) 1935; V. **56**:1189 (Dec.) 1935.

71. Bubert, H. M., and Warner, C. G.: Fatal Asthma: Report of a Case with Bronchial Measurements, J. A. M. A. **104**:1469 (April 27) 1935.

72. Michael, P. P., and Rowe, A. H.: Pathology of Two Fatal Cases of Bronchial Asthma, J. Allergy **6**:150, 1935.

73. Cutler, E. C., and Wood, C. B.: Studies on Endobronchial Occlusion, Surg., Gynec. & Obst. **59**:501, 1934.

stressed by Waldbott and Snell.[74] In my experience the collapse of one lobe has occurred in 2 cases. It is surprising that it does not occur more often, since the immediate pathologic change seems to be the formation of unusually sticky and tenacious exudate. If this exudate can cause partial occlusion, why not complete occlusion?

Studies of the total pulmonary capacity and its subdivisions in patients with emphysema, asthma and pulmonary fibrosis are presented by Kaltreider and his associates [75] in a series of excellent articles. Stress is laid on the ratio between the amount of residual air and the total capacity.

Changes in ventilation as influenced by changes in altitude are discussed by Wittkower and Wolfer,[76] who point out that at high altitudes the complemental air falls and the patient feels better. On the other hand, the vital capacity is also lowered.

Treatment: Treatment has been advanced in several minor ways but without radical change in the general method. The inhalation of epinephrine is the newest procedure. Graeser and Rowe [77] report that when a special 1 : 100 extract of epinephrine is used in a special atomizer many slight attacks can be relieved. My experience corroborates the observation, and the method appears to be useful. On the other hand, when patients use the spray more or less constantly one wonders what may be the ultimate effect of such continuous contraction on the bronchial mucous membrane.

The effect of viosterol on hay fever and asthma has been studied by Rappaport and his associates,[78] who observed that viosterol is an effective adjuvant to the ordinary pollen treatment. Others have used cod liver oil, and there seems little doubt that the increase of vitamins has a beneficial effect. I agree to this and observe that my patients with severe asthma often begin to improve greatly as soon as they reach the point where they can take an adequate amount of a well rounded diet. The

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74. Waldbott, George L.: Allergic Death: VII. Protracted Shock, Arch. Int. Med. **54**:597 (Oct.) 1934. Waldbott, George L., and Snell, A. D.: Pulmonary Lesions Resembling Pneumonia as the Result of Allergic Shock, J. Pediat. **6**:229, 1924.

75. Kaltreider, N. L.; Hurtado, A., and Brooks, W. D. W.: Studies on Total Pulmonary Capacity and Its Subdivisions, J. Clin. Investigation **13**:1027 and 1053, 1934; **14**:81 and 94, 1935.

76. Wittkower, E., and Wolfer, R.: Ueber den Atmungschemismus und-mechanismus der Asthmatiker in Höhenklima und bei Übergang in verschiedene Höhen, Wien. Arch. f. inn. Med. **26**:241, 1935.

77. Graeser, J. B., and Rowe, A. H.: Inhalation of Epinephrine for the Relief of Asthmatic Symptoms, J. Allergy **6**:415, 1935.

78. Rappaport, B. Z.; Reed, C. I.; Hathaway, M. L., and Struck, H. C.: Treatment of Hay Fever and Asthma with Viosterol of High Potency, J. Allergy **5**:541, 1934.

state of the nutrition is important in overcoming chronic infections of every kind.

New varieties of treatment by inoculation have been suggested. Maddox and Back [79] recommend autohemotherapy, with five doses at weekly intervals, each of 10 cc. of blood drawn and reinjected immediately. Their results were good. Johnston [80] uses the patient's urine, "after thorough filtration" and with the addition of a preservative, giving doses every three or four days until a total of 9 cc. has been injected.

In the treatment of rheumatism Cecil and his associates [81] recommend malarial therapy, which was first used by Wagner-Jauregg in 1917 on patients with dementia paralytica. Their patients with rheumatoid arthritis showed good results but had a relapse later. The method should be borne in mind as possible treatment in intractable cases of asthma.

Vaccines administered by mouth have been reintroduced of late. Rockwell, Van Kirk and Powell [82] quote Besredka as saying that the oral administration of vaccine has been successful in cases of typhoid. The authors prepared capsules containing dry organisms, 100 billion each of a rough strain of Pneumococcus type I and a mouse-virulent laboratory strain of hemolytic Streptococcus. One capsule was given every day for a week and then one capsule per week. The capsules were given to 462 persons, and in this group the incidence of colds decreased by 57 per cent of the previous experience, whereas in the control group observed at the same time the incidence of colds during that particular winter decreased 12 per cent of the customary number. Oral desensitization to common foods has been described before, but Keston, Waters and Hopkins [83] report their experiences.

Postural drainage as a treatment of persons with asthma is urged by Shambaugh and Alter,[84] especially for those who have thick, viscid bronchial exudate. Morning and night the patient kneels on a chair, places his hands on the floor and tries to clear the tubes by coughing. In 50 cases the results were good, so good that some of the patients have been free from asthma for four years since the treatment was stopped.

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79. Maddox, K., and Back, R.: Autohemotherapy in the Treatment of Bronchial Asthma, M. J. Australia **1**:277, 1935.

80. Johnston, H. A.: Autodesensitization of Allergic Conditions, California & West. Med. **41**:289, 1934.

81. Cecil, R. L.; Friess, C.; Nicholls, E. E., and Thomas, W. K. S.: Malarial Therapy in Rheumatoid Arthritis, J. A. M. A. **105**:1161 (Oct. 12) 1935.

82. Rockwell, G. E.; Van Kirk, H. C., and Powell, H. M.: Oral Immunization to Colds, J. Immunol. **28**:475, 1935.

83. Keston, B. M.; Waters, Irene, and Hopkins, J. Gardner: Oral Desensitization to Common Foods, J. Allergy **6**:431, 1935.

84. Shambaugh, N. F., and Alter, S. M.: Control of Bronchial Asthma, Science **81**:210, 1935.

The injection of iodized oil into the trachea is advocated by Balyeat and his associates,[85] who point out that the high gravity of the oil forces the bronchial plugs upward and replaces pockets of pus with a nonirritating, nontoxic substance. The results were good in 35 and poor in only 5 cases.

Helium, discovered for medicinal use by Barach,[86] may prove to be a life-saving measure. Helium has an atomic weight of 4 and a density of 0.138. When it is substituted for the nitrogen in the air the mixture is 66 per cent lighter. The light weight and the small density of helium make it possible to force mixtures of helium and oxygen through a small hole in 50 per cent larger quantity than mixtures of nitrogen and oxygen. Helium itself is nontoxic. One difficulty is that the gas is so light and so penetrating that a special form of tent is required for its use.

Somewhat related to the treatment of allergy is an interesting report of the therapeutic use of localized allergy by Garvin and Frumess.[87] A boy of 11 had a bad ulcer of the leg; the authors injected into the surface of the ulcer some potent egg-sensitive serum and the next morning had the boy eat three eggs on an empty stomach. A violent local reaction took place, after which the ulcer began to heal, and in seventeen days the healing was complete.

Epinephrine injected subcutaneously is now, as always, the principal standby. Several of my patients who have taken epinephrine in large quantities and in frequent doses have been noted to have albuminuria, and in one or two instances edema of the ankles was noted also. So far, no formal study has been made of this observation, but it is well to recall the work of Starr,[88] who observed that when the blood supply of the kidney was impeded in rabbits, albuminuria followed. Apparently renal vasoconstriction, which might cause an increase in the normal, intermittent interruption of the glomerular circulation, can result in a disturbance of the glomerular endothelium.

THE NOSE AND THROAT IN ALLERGY

The Warwick[89] method of treatment of hay fever and vasomotor rhinitis is an innovation which has enjoyed a good deal of exploitation.

85. Balyeat, R. M.; Seyler, L. E., and Shoemaker, H. A.: The Diagnostic and Therapeutic Value of the Intratracheal Use of Iodized Oil in Cases of Intractable Asthma, Radiology **24**:303, 1935.

86. Barach, Alvan L.: Use of Helium as a New Therapeutic Gas, Proc. Soc. Exper. Biol. & Med. **32**:462, 1934.

87. Garvin, P. D., and Frumess, G. M.: The Therapeutic Use of Localized Allergy, J. A. M. A. **104**:2333 (June 29) 1935.

88. Starr, I., Jr.: The Production of Albuminuria by Renal Vasoconstriction in Animals and Man, J. Exper. Med. **43**:31, 1926.

89. Warwick, H. L.: Desensitization (Ionization) of Nasal Mucous Membranes for Relief of Asthma, Texas State J. Med. **30**:210, 1934.

By using a solution of electrolytes with the sulfates of zinc, tin and cadmium and an alloy of the same minerals as an electrode, it has been possible to attract electrically the positive metallic ion to the negative pole in the submucosal tissues of the nose. This treatment is now widely used and with a good deal of success, certainly at first. It is too early, however, to know of the end-results. Tobey [90] has used it on 16 patients: Eight had hay fever and obtained 85 per cent relief. Eight had hyperesthetic rhinitis, and 3 of them had asthma as well; in 1, the Warwick method of treatment resulted in complete relief from the asthma for a period of six months, while in 2 others 50 per cent relief lasted for two months and six months, respectively. The two Alexanders [91] watched 25 patients with seasonal or perennial "hay fever" before and after the Warwick treatment and observed that 11 obtained complete and 5 partial relief. The concentration of reagins in the blood was the same before and after treatment and regardless of the result. Evidently the immediate results of the treatment are fairly good. So far, the chief objections are, first, that the machine, the solutions and the electrodes are expensive and, second, that the local reactions which occur at once may last up to forty-eight hours and be of considerable severity.

Meantime, Walsh and Lindsay [92] have made further studies of nasal polypi and state that they can be divided into two types, according to the predominance of eosinophils. Surgical intervention in cases of the different types gives different results; in patients who had polyps with few or no eosinophils the result was distinctly satisfactory, while in other patients whose polyps contained many eosinophils the results were disappointing. A year ago Kern and Schenck [93] concluded that the finding of mucous polyps in the nose warranted the assumption that the patient was of allergic strain. My experience coincides with this in the main, but there are exceptions, and it seems possible that Walsh and Lindsay have offered an explanation of these exceptions. If polyps are present without eosinophils, it may be that polyps do not necessarily and always depend on the repeated insults of some extrinsic factor to which the patient is hypersensitive.

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90. Tobey, H. G.: Experiences in Ionization of the Nasal Mucous Membrane, New England J. Med. **213**:230, 1935.

91. Alexander, H. L., and Alexander, J. H.: Ionization of the Nasal Mucosa: Relationship Between Reagins in the Blood and the Effect of Treatment, J. Allergy **6**:240, 1935.

92. Walsh, T. E., and Lindsay, J. R.: Cytology of Nasal Polyps, Arch. Otolaryng. **20**:649 (Nov.) 1934.

93. Kern, R. A., and Schenck, H. P.: Allergy a Constant Factor in the Etiology of So-Called Mucous Nasal Polyps, J. Allergy **4**:485, 1933.

DRUG ALLERGY

In a special article written for *The Journal of the American Medical Association* Kracke and Parker [94] describe the relationship of drug therapy to agranulocytosis. The bibliography is excellent and useful. About the same time, there appeared an article by Hunter [95] entitled "Agranulocytosis: Drug or Protein Allergy As a Cause of Agranulocytosis and Certain Types of Purpura." Hunter has also reviewed the literature and has done it completely, so that his work will be the basis for other articles on the subject for some time. According to Hunter, agranulocytosis was first described by Schultz [96] in 1922. This was twelve years before Madison and Squier [97] published their first paper in October 1933 and thus did so much to develop the whole field of drug allergy. In reviewing the immense amount of material Hunter points out that in most cases the symptoms of agranulocytosis follow the second course of treatment with a particular drug. The patient has taken this drug before and then allows an interval of time to elapse before taking it again. It is the second dose which causes the difficulty. If always true, the fact is important, because it alone is strong support of the opinion that agranulocytosis is the result of allergic reaction. A case in point is that described by Walter.[98] Hexylresorcinol was applied persistently to the skin over a period of five months, and then came a period without further use of the drug. Twenty-six months later a severe dermatitis resulted from a single brief contact with hexylresorcinol. Meantime, it is interesting to compare Vaughan's observations on the leukopenic index described previously with this other new knowledge. Herz [99] points out that the difference in the ability of various drugs to cause agranulocytosis depends on their different chemical structure, regardless of whether the hydrogen atom is replaced by another radical. In aminopyrine, for example, the NH radical is replaced by a benzene ring, and the product is frequently the cause of

94. Kracke, R. R., and Parker, F. P.: The Relationship of Drug Therapy to Agranulocytosis, J. A. M. A. **105**:960 (Sept. 21) 1935.

95. Hunter, F. T.: Agranulocytosis: Drug or Protein Allergy as a Cause of Agranulocytosis and Certain Types of Purpura, New England J. Med. **213**: 663, 1935.

96. Schultz, W.: Ueber eigenartige Hakerkrankungen, Deutsche med. Wchnschr. **48**:1495, 1922.

97. Madison, F. W., and Squier, T. L.: Primary Granulocytopenia After Administration of Benzene Chain Derivatives, J. A. M. A. **101**:2076 (Dec. 23) 1933.

98. Walter, C. W.: Idiosyncrasy to Hexylresorcinol, J. A. M. A. **104**:1897 (May 25) 1935.

99. Herz, L. F.: The Rôle of Amidopyrine in the Etiology of Granulocytopenia with Special Reference to Its Chemical Structure, J. Lab. & Clin. Med. **20**:33, 1934.

disturbances of the blood. Acetanilid, acetphenetidin, salicylic acid and acetylsalicylic acid have somewhat similar chemical structures and may cause violent reactions in sensitive patients. Herz' article includes the graphic formulas of many common drugs and is therefore instructive. Francis, Ghent and Bullen [100] report the case of a man, aged 27, who died thirty hours after taking 10 grains (0.65 Gm.) of acetylsalicylic acid.

ALLERGIC CUTANEOUS DISEASE

Sulzberger, Wise and Wolff [101] present a tentative classification of allergic dermatoses, the "eczemas," laying stress on atopic dermatitis, with its characteristic distribution and its characteristic reactions comparable to those of hay fever and asthma and often dependent on heredity. In cases of atopic dermatitis the exciting cause reaches the skin through the blood stream underneath. In contrast to it is contact dermatitis, which is a local sensitiveness of the skin itself, the difficulty being precipitated by direct contact with the offending agent. Another type of dermatitis is represented by the reaction to tuberculin and to trichophytin, with its definite clinical picture and with responses which are delayed for twenty-four hours. In certain cases the reactions to patch tests, so characteristic of contact dermatitis, have resulted in acneform responses. In another paper Sulzberger [102] suggests that acne vulgaris is merely a response to a pilosebaceous irritant which comes from within the body. In this way he would explain the eruptions caused by bromide and iodide. Tuberculous acne probably belongs in the same category. Just how these observations can be correlated with the knowledge that acne is so common at adolescence and therefore is concerned with the gonads is a little difficult. Sulzberger suggests, however, that further experiments might demonstrate a hypersensitiveness of the pilosebaceous apparatus to various hormones, and the effect is therefore something more than simple stimulation of the apparatus by these same hormones.

Hill [103] gives an excellent review of his study of 900 cases of eczema in infants and young children, most of them in the group of atopic dermatitis. If the exciting cause is borne by the blood there is no reason that the conception of it should be limited to foods. Dusts which are

100. Francis, N.; Ghent, O. T., and Bullen, S. S.: Death from Ten Grains of Aspirin, J. Allergy **6**:504, 1935.

101. Sulzberger, M. B.; Wise, Fred, and Wolf, Jack: Allergic Dermatoses, J. A. M. A. **104**:1489 (April 27) 1935.

102. Sulzberger, M. B.: Acneform Responses to Patch Tests: Follicular and Papulopustular Reactions to Selectively Pilosebaceous Irritants, Arch. Dermat. & Syph. **30**:566 (Oct.) 1934.

103. Hill, Lewis W.: Chronic Atopic Eczema (Neurodermatitis) in Childhood, J. A. M. A. **103**:1430 (Nov. 10) 1934.

inhaled also reach the blood stream, and in a number of cases it has been possible to show that the outbreak of eczema did bear a direct relation to changes in environment; so pollens, animal danders and the dust of furniture and bedding should always be considered in the etiology of atopic dermatitis. In other cases dusts can cause contact dermatitis. These points are brought out in a second paper by Hill [104] and are illustrated by reports of the cases of the interesting group of patients with contact dermatitis due to pollen.

Brunsting and Anderson [105] report 18 cases of ragweed dermatitis. Their article has excellent pictures. In my experience these patients are easy to care for because, once the diagnosis is made, treatment with the ether-soluble fraction of the ragweed pollen dissolved in olive oil is so effective that only three or four doses are necessary.

Sensitization of the skin by artificial means has been studied further by Straus,[106] who was able previously to sensitize the skin of new-born infants to poison ivy by direct application of the extract. When drop doses were given by mouth on each of five days symptoms did not result and sensitization by patch test could not be demonstrated later, but when the 10 per cent extract was injected subcutaneously 1 of the 10 infants showed a positive reaction to a patch test. On the whole, however, it can be said that sensitiveness of the skin is produced only by treatment of the skin itself.

The sensitization of guinea-pigs to arsphenamine and other arsenic compounds has given varying results, apparently dependent on whether the experiments were made in Boston, New York or Zurich. The cause of the discrepancy has been unknown and remains so, in spite of the careful controls which Sulzberger and Simon [107] have instituted.

In one experiment Sulzberger and Oser [108] fed their guinea-pigs large amounts of cevitamic acid and noted that the marked increase of vitamin C in the diet did increase the percentage of positive results to some extent.

The grouping of patients with cutaneous disease into one or the other category may be dangerous for the reason that different types

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104. Hill, Lewis W.: Sensitivity to Environmental Allergens in Infantile Eczema, New England J. Med. **213**:135, 1935.

105. Brunsting, L. A., and Anderson, C. R.: Ragweed Dermatitis: A Report Based on Eighteen Cases, J. A. M. A. **103**:1285 (Oct. 27) 1934.

106. Straus, H. W.: Experimental Study of the Etiology of Dermatitis Venenata, J. Allergy **5**:568, 1934.

107. Sulzberger, M. B., and Simon, F. A.: Arsphenamine Hypersensitiveness in Guinea Pigs, J. Allergy **6**:39, 1934.

108. Sulzberger, M. B., and Oser, B. L.: Influence of Ascorbic Acid of Diet on Sensitization of Guinea Pigs to Neoarsphenamine, Proc. Soc. Exper. Biol. & Med. **32**:716, 1935.

of dermatitis may occur together in the same patient. A patient with an atopic type of sensitiveness may also have a skin which is susceptible to reaction on direct contact, and it is with this idea that the use of patch tests, even in typical allergic dermatitis, has been suggested. On the whole, however, Hill has been unable to confirm the rather enthusiastic reports of Peck and Salomon.[109]

Fungous infections of the skin illustrate this point in a different way. Browning[110] expresses the opinion that the symptoms of ringworm are a complication of hypersensitiveness. Many of his patients had other manifestations of allergy besides ringworm, and treatment on the basis of this allergy has brought good results.

Traub and Tolmach[111] treated 135 patients having dermatophytosis with intradermal injections of trichophytin. Apparent cure was obtained in 14 patients, and 58 others showed some improvement, but it is evident that the method leaves much to be desired.

In the meantime, Adamson[112] suggests that psoriasis has a possible allergic background. He collected the scales from psoriatic lesions, washed them with ether and then made various extracts in watery saline solutions. Intradermal tests with these extracts caused a negative reaction in 10 persons with normal skin but caused a positive reaction in each of 6 patients with psoriasis. The apparent sensitiveness could not be transferred to a normal recipient.

OTHER MANIFESTATIONS OF ALLERGY

Migraine.—Vallery-Radot and Hamburger[113] have an excellent article on the probable physiology of migraine. Scotoma, transient palsy and heminanopia suggest a definite lesion in the cortex, perhaps near the optic chiasm. Moreover, the average attack is short, and the lesion must therefore be "reversible" and not a true destruction of the tissue. Other studies concern the direct observation of the cerebral arteries following attempts to produce spasm or dilatation by drugs. In addition, the authors review the literature on the sympathetic system, pointing out that the cerebral circulation as a whole has a regulator mechanism con-

109. Peck, S. M., and Salomon, G.: Eczema of Infancy and Childhood; I. Contacts as Etiologic Agents, with Particular Reference to Feathers, Am. J. Dis. Child. **46**:1308 (Dec.) 1933.

110. Browning, W. H.: Ringworm of Extremities Due to Allergic Unbalance, New Orleans M. & S. J. **87**:747, 1935.

111. Traub, E. F., and Tolmach, J. A.: Dermatophytosis: Its Treatment with Trichophytin, Arch. Dermat. & Syph. **32**:413 (Sept.) 1935.

112. Adamson, W. B.: Psoriasis as Possible Allergic Manifestation, J. Allergy **6**:294, 1935.

113. Vallery-Radot, P., and Hamburger, J.: Pathogénie de la migraine, Biol. méd. Paris **24**:235, 1934.

trolled chiefly by the cervical portion of the sympathetic system. If the sympathetic trunk is severed on one side the regulator mechanism no longer functions, and under these conditions epinephrine can produce a much greater vasoconstrictor action. Certain drugs, such as ergotamine, which affect the sympathetic nervous system can in this way enhance the action of epinephrine.

These observations find some confirmation in the studies from Forbes' laboratory at Harvard. Here, Finley [114] made trephine holes in the skull of sensitized guinea-pigs and then made direct observations on the changes in caliber of the pial vessels during anaphylactic shock. His observations are contrary to expectation because during shock the pial vessels showed no constriction but definite dilatation and cyanosis, and this effect was specific, because the injection of serum into nonsensitive animals produced no such change. Later however, this dilatation proved to depend not on anaphylaxis but on asphyxia, because in another experiment the clamping of the trachea resulted in a similar change in the pial vessels.

Foster Kennedy [115] has already laid stress on various focal symptoms, not only in migraine but following the use of therapeutic serums. New laboratory studies confirm the conclusions which Kennedy drew from his clinical observations, namely, that edema of the brain is often localized.

Vaughan [116] continued his clinical study of migraine. Fifty-one of his patients were relieved to a considerable extent by the elimination of specific foods and dusts, according to the methods of clinical allergy.

Epilepsy is, in many respects, analogous to migraine, and Forman [117] reports 10 cases in which the attacks of unconsciousness were found to depend on sensitiveness to a specific food.

Urticaria: Fink and Gay [118] report on 170 patients with urticaria whom they have followed for from two to ten years. Urticaria due to cold is an interesting condition, heretofore shrouded in some mystery.

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114. Finley, K. H.: Changes in Caliber of Pial Vessels in Guinea Pigs During Anaphylactic Shock, J. Immunol. **27**:169, 1934.

115. Kennedy, Foster: Migraine: A Symptom of Focal Brain Edema, New York State J. Med. **33**:1254 (Nov. 1) 1933; Nervous Complications Following the Use of Therapeutic and Prophylactic Serums, Tr. Am. Neurol. A., 1928, p. 410.

116. Vaughan, Warren T.: An Analysis of the Allergic Factor in Recurrent Paroxysmal Headaches, J. Allergy **6**:365, 1935.

117. Forman, J.: Atopy as Cause of Epilepsy, Arch. Neurol. & Psychiat. **32**:517 (Sept.) 1934.

118. Fink, Arthur I., and Gay, Leslie N.: A Critical Review of One Hundred and Seventy Cases of Urticaria and Angioneurotic Edema Followed for a Period of from Two to Ten Years, Bull. Johns Hopkins Hosp. **55**:280, 1934.

Levine [119] reviews the literature with considerable care. The cases fall into two groups: in one the sensitiveness is a purely local phenomenon of the skin, and in the other the cutaneous manifestation is simply a part of an underlying systemic disturbance, the lesions representing an aggravation of Lewis' triple response. In spite of his systematic study, however, Levine is bound to confess that he could not apply his knowledge to all the cases at hand and he could not place all of them in one group or the other.

Other Symptoms.—Other symptoms have been linked with allergy. Ryle [120] describes certain abdominal and circulatory disturbances to which the theories of allergy might have application, especially if certain postulates are fulfilled. These postulates include evidence of allergy in the family background, other allergic manifestation in the patient, such as cutaneous lesions, hay fever or asthma, or perhaps simply that the patient knows of his idiosyncrasy to some food, drug or extraneous substance and, finally, some evidence that the symptoms, however bizarre, do come and go in accordance with changes in environment or diet.

Freedman [121] reports another case of anaphylactic shock. A boy, aged 6 years, with a history of asthma and eczema, was given diphtheria antitoxin. On the sixth day, severe asthma developed, and on the ninth day, urticaria. On the twentieth day, the boy came to the clinic, where his sensitiveness to horse serum was tested by the injection of 0.05 cc. intracutaneously. In two minutes he was covered with patches of urticaria, and in eight minutes he was dead.

Deissler and Higgins [122] describe the reactions of the whole filled gallbladders of sensitive guinea-pigs when antigen is injected, saying that the pressure in the gallbladder is raised to three times the normal figure. The contraction of the sphincter is evidently greater than that of the rest of the muscle.

Ocular cataracts in young persons were associated with allergy in 3 cases reported from the Mayo Clinic by Daniel.[123]

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119. Levine, H. D.: Urticaria Due to Sensitivity to Cold: Survey of the Literature and Report of Case with Experimental Observations, Arch. Int. Med. **56**:498 (Sept.) 1935.

120. Ryle, J. A.: Observations on Abdominal and Circulatory Phenomena of Allergy, Lancet **1**:1257, 1935.

121. Freedman, Harold J.: Acute Anaphylactic Shock Following Intracutaneous Test for Sensitivity to Horse Serum, New England J. Med. **212**:10, 1935.

122. Deissler, K., and Higgins, G. M.: Effect of Anaphylactic Shock on Biliary System, Proc. Staff Meet., Mayo Clin. **9**:678, 1934.

123. Daniel, Ruby K.: Allergy and Cataracts, J. A. M. A. **105**:481 (Aug. 17) 1935.

Cleveland White [124] claims that acneform eruptions of the face may depend on hypersensitiveness to a specific food and describes 32 cases in support of his theory.

Reaction to Tobacco.—This problem has been advanced a little further by Chobot,[125] who has collected all the figures from the previous works of Harkavy and Sulzberger. Between 70 and 80 per cent of patients with thrombo-angiitis obliterans are sensitive to tobacco, but the trouble is that the controls are likewise sensitive in many instances. Chobot studied the reactions of allergic children to tobacco and found that only 6 of 63, or 11 per cent, gave a negative reaction. All the others (89 per cent) gave a positive reaction in some degree. Passive transfer was attempted with the blood serum of 4 of these children but never with success. An attempt to sensitize guinea-pigs and test the sensitiveness by the uterine strip reaction was negative.

New Allergens.—The list increases constantly.

Karaya gum, used in hand lotions, in printing and especially in fluid for waving hair, has caused a reaction in 2 interesting cases reported by Bullen [126] and Feinberg,[127] respectively.

Chicle in chewing gum caused symptoms and positive reactions in a patient of Kleinman.[128]

Bennett [129] had a patient of 10 years who had the habit of eating paper. The child lost weight, was in poor general condition and later had asthma. At that time, cutaneous tests made with the paper extract caused a positive reaction.

Lycopodium is used in a new powder for an oily scalp, and in a patient whose case is reported by Lambright and Albaugh,[130] perennial hay fever developed from this powder.

Camomile (Anthemis cotula) grows throughout the United States as a weed. Rowe [131] had a patient who had a severe rash on his face

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124. White, Cleveland: Acneform Eruptions of the Face: Etiologic Importance of Specific Foods, J. A. M. A. **103**:1277 (Oct. 27) 1934.

125. Chobot, R.: The Significance of Tobacco Reactions in Allergic Children, J. Allergy **6**:383, 1935.

126. Bullen, S. S.: Perennial Hay Fever from Indian Gum (Karaya Gum), J. Allergy **5**:484, 1934.

127. Feinberg, S. M.: Karaya Gum Asthma, J. A. M. A. **105**:505 (Aug. 17) 1935.

128. Kleinman, A. I.: Allergy to Chicle: Preliminary Report, J. A. M. A. **104**:455 (Feb. 9) 1935.

129. Bennett, T.: Case Report: Bronchial Asthma Due to Paper Sensitivity, New England J. Med. **213**:121, 1935.

130. Lambright, G. L., and Albaugh, R. P.: Perennial Hay Fever from Lycopodium, J. Allergy **5**:590, 1934.

131. Rowe, Albert H.: Camomile (Anthemis Cotula) as a Skin Irritant, J. Allergy **5**:383, 1934.

due to direct contact with this plant. Rowe's article contains several good pictures.

Gaillardia caused dermatitis in 3 patients whose cases were reported by Rostenberg and Good.[132] All three had handled gaillardia flowers.

Emeraude perfume caused dermatitis in a patient whose case was reported by Tobias.[133]

Dust of insect origin receives continued attention and no doubt should receive more. Randolph [134] and MacDermot [135] have each written on the subject of hay fever and asthma dependent on the emanations from May-flies (Ephemerida).

Two other reports are of more general interest. Held and Goldbloom [136] describe the case of a patient with pernicious anemia in whom generalized itching with wheals and subcutaneous swellings developed after the injection of liver extract. Later, however, the woman was able to take cooked liver by mouth, and still later, small but increasing doses of liver extract injected subcutaneously each day resulted in a disappearance of the trouble. During this treatment, the eosinophil count dropped from 16 to 2 per cent.

Simon [137] describes the cases of several patients hypersensitive to pituitary extract, commenting on the fact that like the reaction to lens protein, that to pituitary substance is another illustration of the fact that sensitiveness can develop to a substance present in the patient's own body, that is to say, of homologous origin.

SUMMARY

During the year, a good deal has been accomplished. In the future chemical studies of those substances which produce allergic symptoms to trace the nature of the skin test-active factors still further and to compare them one with another will be helpful. Besides that, however, one must know more about the first development of allergy. How is

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132. Rostenberg, Adolph, Jr., and Good, C. K.: Gaillardia Dermatitis, J. A. M. A. **104**:1496 (April 27) 1935.

133. Tobias, Norman: Emeraude Perfume Dermatitis, J. A. M. A. **104**:1322 (April 13) 1935.

134. Randolph, H.: Allergic Response to Dust of Insect Origin, J. A. M. A. **103**:560 (April 27) 1934.

135. MacDermot, H. E.: Case Due to May Flies (Ephemerida), Canad. M. A. J. **31**:408, 1934.

136. Held, I. W., and Goldbloom, A. A.: Addison-Biermer's Anemia (Pernicious Anemia): Report of Case Showing Allergic-Like Phenomena to Liver Extract, J. A. M. A. **96**:1361 (April 25) 1931.

137. Simon, Frank A.: Hypersensitiveness to Pituitary Extract, J. A. M. A. **104**:996 (March 23) 1935.

the body sensitized? By what chemical combination? How and why does the first reaction to contact take place? Infections of the respiratory tract are concerned with this process—there is reason to think of this—but how are the effects achieved? And then, the same old question: Why is it that of all the many persons exposed to a dust, like ragweed pollen, for example, sensitiveness develops in only a few?

After sensitiveness has developed and symptoms occur, what is the treatment? What is the nature of "desensitization"? How long does it last?

These are some of the problems, and the great difficulty is that whatever may be the findings, the results of experiments on animals do not always apply to man and, further, that regardless of what one does, the nature and the degree of sensitiveness in the particular patient are prone to change spontaneously. The hay fever may be outgrown. Any results obtained in allergy, whether experimental or therapeutic, are always hard to control.

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A CRITICAL REVIEW OF THE LITERATURE ON CHRONIC RHEUMATISM

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As the diseases to be discussed are usually designated by the practitioner as chronic rheumatism, this title is chosen. Under this title are two distinct diseases, each differing from the other in etiology, pathology and clinical signs and symptoms. The only points in common are chronicity and involvement of the joints.

As the mortality from either type is practically nil, there are no statistics in this country to indicate the incidence of the two diseases. In England, with its industrial insurance, statistics are available. Glover [1] reported: ". . . In any 1,000 insured males of all ages there will be found one case of rheumatoid arthritis and three cases of osteo-arthritis. . . . In any 1,000 insured females of all ages, we should expect three cases of rheumatoid arthritis and two of osteoarthritis." The figures on osteo-arthritis include only the cases of persons who consult the panel doctor on account of discomfort from the disease. Its actual incidence is far above that mentioned, as only a small percentage of persons with osteo-arthritis suffer from it.

Antiquity of Chronic Rheumatism.—Osteo-arthritis is the most ancient disease of which there is a record. Moody [2] has called attention to the great frequency of this type of arthritis in the spines of prehistoric animals. As this is a degenerative rather than an infective type of arthritis and as it arises from wear and tear which represents long continued mild trauma or acute trauma to an articulation, its frequency in the skeletons is readily understood.

Not a single instance of rheumatoid arthritis of the extremities was noted in 35,000 Egyptian mummies carefully examined for evidence of disease. Jones [3] reported that practically every adult skeleton showed osteo-arthritis of the spine. This can probably be accounted for, at least in part, by the custom of carrying heavy loads on the head. Hrdlička [4] reported the not infrequent presence of osteo-arthritis of the spine in ancient Indian remains.

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1. Glover, J. A.: A Report on Chronic Arthritis, Reports on Public Health and Medical Subjects, Ministry of Health, no. 52, London, His Majesty's Stationery Office, 1928.

2. Moody, R. L.: Paleopathology, Urbana, Ill., University of Illinois Press, 1923.

3. Jones, F. W. J.: Archeological Survey of Nubia **2**:26, 1907-1908.

4. Hrdlička, A. J.: J. Acad. Nat. Sc. Philadelphia **14**:178, 1909.

CLASSIFICATION

Confusion in classification has played an important part in retarding the knowledge of this group of diseases. The medical profession has been tardy in recognizing or at least in applying the splendid studies of Nichols and Richardson,[5] who from their exhaustive pathologic studies demonstrated that chronic rheumatism could be divided into two types. They stated: "Our own studies have convinced us that these joint lesions can be divided with great definiteness into two pathological groups: 1, Those which arise from primary proliferative changes in the joints, chiefly in the synovial membrane and in the perichondrium. 2, Those which arise primarily as a degeneration of the joint cartilage." One has the appearance of a chronic infective disease; the other, that of a degenerative disease.

Only in the last decade has a united effort been made in this country to obtain a classification based on pathologic changes and clinical manifestation. The American Committee on Chronic Rheumatism, fathered by Dr. Ralph Pemberton and Dr. Robert Osgood, deserves a great deal of credit for creating an increased interest in this group of diseases.

At the International Congress on Chronic Rheumatic Diseases held at Liége a few years ago, a classification in French, German and English was adopted. The following is the English terminology: (1) rheumatoid arthritis and (2) osteo-arthritis. These terms for the two types have been in common use in England for many years. Synonymous terms for rheumatoid arthritis are infective periarthritis, atrophic arthritis and arthritis deformans. Unfortunately, the term arthritis deformans is used in Germany for osteo-arthritis. The term coined by Nichols and Richardson was proliferative arthritis. Hypertrophic arthritis is synonymous with osteo-arthritis. The name given to this type by Nichols and Richardson was degenerative arthritis.

In the present review the terms used for the two diseases are rheumatoid arthritis and osteo-arthrosis. Arthrosis is a more accurate descriptive term for this type than arthritis; it was introduced in 1913 by Frederich Müller of Munich and is widely used in Germany. For that reason I have adopted it rather than the term degenerative arthrosis. The simpler the classification, the more readily it will be understood and adopted by the medical profession.

Some German writers subdivide rheumatoid arthritis into a primary and a secondary type. By secondary rheumatoid arthritis they mean the condition that begins as acute rheumatic fever and gradually develops into a chronic type. This form appears to be common in Germany but is rare in this country. As far as I can recall, I have seen only 1 case.

5. Nichols, E. H., and Richardson, F. S.: J. M. Research **21**:144, 1909.

PATHOLOGY

Rheumatoid Arthritis of the Extremities.—From the standpoint of etiology, emphasis should be placed on the early changes. The later changes may be due to trauma, unequal pressure on the cartilage of the joint or ligamentous traction due to the deformity. This phase of the subject will be discussed later with mixed forms of arthritis.

In the early stage of rheumatoid arthritis there is a round cell infiltration beginning at the junction of the synovial fringe with the articular cartilage. The cellular infiltration gradually extends over the surface of the joint until the whole or only the peripheral portion of the cartilage is covered by a highly vascular membrane resembling granulation tissue. This pannus invades and destroys the underlying cartilage, which is replaced by connective tissue and later by fibrous tissue. Nichols and Richardson stated that not all the cartilage under the pannus is destroyed; circumscribed areas may remain intact.

The round cell infiltration is not confined to the articular surfaces but extends into the periarticular structures and accounts, at least in part, for the characteristic spindle-shaped deformitiy, best observed in the fingers. In the periarticular structures fibrous changes develop and may be a contributory factor in producing ankylosis.

Simultaneously with the synovial changes, there is marked proliferation due to round cell infiltration of the villi. The slender villous outgrowths later undergo endarteritis obliterans which results in necrosis. In later stages of the disease, polypoid growths (some sessile, others pedunculated) resembling those observed in osteo-arthrosis, but rarely so extensive, may develop. Nichols and Richardson stated that such growths may arise from the pannus or from the synovium.

Simultaneously with the round cell infiltration of the synovium, and sometimes subsequent to it, similar round cell infiltration with later formation of connective and fibrous tissue may be observed in the adjacent subcancellous tissue of the epiphysis, and this extends and destroys the adjacent cartilage.

The end-result of the changes in the joint may be fibrous ankylosis or, in case the cartilage is completely destroyed in any area so that the exposed bones come in contact, bony ankylosis. Nichols and Richardson did not study rheumatoid arthritis of the spine.

Rheumatoid Arthritis of the Spine (Spondylitis Ankylopoietica).—When rheumatoid arthritis involves the spine, there may develop unusual pathologic changes, largely in the nature of sequelae. As rheumatoid arthritis first involves the synovium and as the intervertebral disk does not have a synovium, the disease attacks the articulation of the transverse processes and the ribs. The pathologic changes are probably the same as those in the extremities. The articulations probably rather early

become ankylosed. As in the extremities, there are early atrophic changes in the involved vertebrae. Later there may be a series of pathologic changes directed toward firm ankylosis of the involved portion of the spine. The sequelae, when they develop, do not appear until considerable time has elapsed. The exact order or sequence of the changes is not definitely known, but they probably appear in the following order: (1) ossification of the intervertebral ligament, especially the anterior longitudinal ligament; (2) invasion by the spongiosa of a vertebra of the adjacent central portion of the disk and penetration through it to the spongiosa in the neighboring vertebra, and (3) possible ossification of the periphery of the disk. The complete structural change creates in the involved portion of the spine an anatomic structure resembling a long bone. The anatomic changes produce a poker spine. The changes are not confined to patients with rheumatoid arthritis. They may arise from other infections. The subject will be discussed under etiology.

Osteo-Arthritis of the Extremities.—In their investigations of this disease Nichols and Richardson apparently studied only the senescent type, in which changes are due to long continued mild trauma. They did not discuss cases in which the disease arises from acute injury, as for instance the baseball finger. In such cases the damage to the cartilage is followed by a sequence of changes similar to that of the senescent form. Nichols and Richardson did not study osteo-arthrosis of the spine, in which another factor is at least largely responsible for the formation of osteophytes. Fisher [6] defined osteo-arthrosis as follows: "Osteoarthritis does not constitute a disease sui generis, but is rather the series of physiological or pathological changes that occur in a joint when it is subjected to prolonged or oft-repeated injury, either mechanical or toxic, but of a moderate degree of intensity." He failed to mention that acute severe injury may give rise to similar changes.

Normal cartilage on bending shows striae. Nichols and Richardson reported that the earliest lesion was fibrillation of the cartilage. Fibrous tissue forms in the striae, and this results in a ridging of the cartilage, followed in turn by vertical cracking. The changes are most marked in the central cartilage of the surface of the joint, due probably to poor nutrition, as the cartilage does not contain blood vessels and is nourished by diffusion. Following the fibrous changes there is irregular degeneration of the cartilage, which gives a pitted appearance to the surface. The bottom of the pit may show exposed bone. The intervening area of intact cartilage may proliferate and later show ossification. The peripheral cartilage may remain normal for years after the central degeneration. Sooner or later, however, there is cartilaginous hyperplasia,

6. Fisher, A. G. B.: Chronic (Non-Tuberculous) Arthritis, New York, The Macmillan Company, 1929, p. 192.

which results in lipping, and later ossification develops which gives rise to osteophytes, which characterize this type of arthritis. Fisher expressed the opinion that the proliferation of the peripheral cartilage is a physiologic response to increase the surface of the joint.

In contradistinction to rheumatoid arthritis, changes in the synovium appear late and take the form of villous proliferation. Existing villi become hypertrophied, and many new villi arise from the synovium. Chondromas may develop in the villi. These may later become detached and give rise to loose bodies. Their presence may account for the recurrent synovitis seen in patients with this condition. The crunching sounds heard in cases of osteo-arthrosis of the knee are due largely to rubbing together of the villi.

Bony or fibrous ankylosis is practically unknown. Atrophy of muscle and skin is not present, nor is there ischemia of the skin.

When the central cartilage is acutely injured it undergoes necrosis. Fisher shaved a very thin layer of central cartilage from a rabbit's knee and several weeks later killed the animal. He observed that the periphery of the articulation showed cartilaginous lipping and that the central cartilage was necrotic. Injury of the cartilage by other means, as by the injection of acid, will produce similar changes. Osteo-arthrosis can be produced readily experimentally, but no one has been able to produce experimental rheumatoid arthritis.

Osteo-Arthrosis of the Spine.—Osteo-arthrosis of the extremities has its origin in the articular cartilage. The intervertebral disk has only a thin fibrocartilaginous plate between it and the vertebra. The pathology of this type of arthrosis when it involves the spine requires separate attention.

The most important pathologic studies of the disease have been made in Germany. Schmorl and Junghanns,[7] with their careful study of 10,000 spines removed at autopsy, have supplied a valuable fund of information. The monograph of Anton Fischer has summed up, and added to, the knowledge of the condition. I[8] recently discussed the present knowledge of the subject.

Jones[9] made a careful study of the spines of a large number of natural mummified Nubian remains. His observations have since been confirmed by Schmorl. He took the position that the osteophytes develop not on the rim of the vertebra but slightly above and corresponding to points of attachment of the fibers of the anterior longitudinal ligament.

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7. Schmorl, G., and Junghanns, H.: Die gesunde und kranke Wirbelsäule im Roentgenbild, Leipzig, Georg Thieme, 1932.

8. Miller, Joseph L.: Chronic Rheumatic Diseases of the Spine, Arch. Int. Med. **54**:161 (Aug.) 1934.

9. Jones,[3] p. 271.

The spine of man has not adjusted itself to the upright posture, as is shown by the pathologic changes which develop with increasing years.

The intervertebral disk is made up of two closely related but somewhat different structures, the annulus fibrosus and the nucleus pulposus. They function as shock-absorbers and also assist in the rotation of the spine. Both of the structures are formed by interlacing fibrous tissue, with a mucoid fluid in the interspaces. Both begin to show degenerative changes as early as the third decade of life. Schmorl noted that 10.7 per cent of the spines removed from bodies of persons between 20 and 30 years of age showed evidence of pathologic changes.

The earliest degenerative changes in the disk are noted in the nucleus pulposus. It loses its fluidity, and the fibers become desiccated and finally disintegrate. The elastic ball is replaced by a solid mass, which may later become calcified.

Somewhat later the annulus undergoes similar degenerative changes. As a consequence of these changes the disk becomes thinned and loses its resiliency. Under normal conditions the fibers of the annulus play an important rôle in the fixation of the vertebra. There is increased mobility of the vertebra, with the destruction of the annulus. Schmorl stated that he has never seen osteophytes adjacent to a normal disk. The increased mobility of the vertebra is the most important etiologic factor in the formation of osteophytes. Rarely does mere impingement of the vertebra account for the formation of spurs. The increased mobility causes increased traction on the intervertebral ligaments, especially the anterior longitudinal ligament. As a result of the strain, periosteal trauma occurs at the points where the fibers are attached to the bone. It is in this region that osteophytes develop. Not infrequently one finds bony spurs along the entire course of the insertions of a ligament, evidence that traction as well as pressure may be responsible for osteoarthrosis. Acute trauma to a vertebra or sudden severe damage to a disk may be responsible for the formation of osteophytes.

Anton Fischer has expressed the opinion that the formation of osteophytes on a vertebra is a physiologic response directed toward reconstruction of a spine which has become functionally inefficient. The primary objective is to effect a bridging of the interspace between the vertebrae and render the spine rigid.

Osteomyelitis of a vertebra following typhoid may be followed later by a growth of osteophytes from the damaged and adjacent vertebrae, which results in complete bridging. Dr. Hollis E. Potter showed me a roentgenogram in a case in which the development of such changes had been followed by repeated roentgen observations of the spine.

From these findings one may conclude that a poker spine following typhoid may be due to spondylitis ankylopoietica or to localized bridging by osteophytes, which arise as a result of osteomyelitis of a vertebra.

Calcium Metabolism.—Hastings and Greene [10] made determinations of the calcium content of the blood in 50 cases of rheumatoid arthritis and 50 cases of osteo-arthrosis. In the cases of rheumatoid arthritis the calcium content was normal; in the cases of osteo-arthrosis there was a slight reduction, which the authors thought might be due to the greater average age of the patients.

Cholesterol.—Hastings and Bruger [11] observed that the total cholesterol content of the blood tends to be slightly reduced in rheumatoid arthritis and increased in osteo-arthrosis. The authors venture the opinion that this is evidence that rheumatoid arthritis is of infective origin and osteo-arthrosis of degenerative origin.

ETIOLOGY

Rheumatoid Arthritis.—The presence of round cell infiltration in the synovium in the early stages of the disease is evidence that rheumatoid arthritis is an inflammatory disease of probable bacterial origin.

A number of observers have made sedimentation tests on the blood and have noted a positive reaction in a high percentage of cases. The same group noted a negative reaction in cases of osteo-arthrosis. Dawson and Boots [12] reported that the sedimentation rate parallels to a high degree the severity and extent of the arthritic process.

Dawson and Olmsted [13] have made careful studies of the agglutination reaction in 66 cases of rheumatoid arthritis and have also carried out tests in a series of controls. In cases of active rheumatoid arthritis the serum agglutinated in a high titer all strains of hemolytic streptococci. The authors observed that the special hemolytic streptococcus isolated by Cecil from the blood stream was not agglutinated in a higher titer than other strains. In 50 controls (18 cases of osteo-arthrosis) agglutination occurred in 2 and only in a low titer. Thirty-one strains of other organisms failed to be agglutinated.

Dawson, Olmsted and Jost [14] made a comparative test of agglutinins and precipitins against hemolytic streptococci in 71 cases of rheumatoid arthritis. They noted a close but not absolute agreement in the capacity of serum from patients with rheumatoid arthritis to agglutinate and precipitate various strains of hemolytic streptococci. Of the controls agglutination occurred in only 5 per cent in a titer of 1 : 160.

There is abundant clinical evidence that the disease is infective. Still's disease (which is rheumatoid arthritis of childhood) causes not

10. Hastings, E. F., and Greene, C. H.: J. Lab. & Clin. Med. **20**:929, 1935.
11. Hastings, E. F., and Bruger, M.: J. Lab. & Clin. Med. **20**:675, 1935.
12. Dawson, M. H., and Boots, R. H.: New England J. Med. **208**:1030, 1933.
13. Dawson, M. H., and Olmsted, W.: J. Immunol. **29**:189, 1932.
14. Dawson, M. H.; Olmsted, W., and Jost, E. L.: J. Immunol. **27**:385, 1934.

only marked inflammation of the joints but also fever, leukocytosis, lymphadenitis and frequently enlargement of the spleen. The disease in adults is more insidious in onset but nevertheless presents evidence of an inflammatory reaction. The course of the disease, with remissions and later recurrences, speaks for its infective origin.

The problem of positive results of blood cultures is a moot question. Some competent bacteriologists have obtained positive results of cultures in 60 per cent of cases.[15] There are many other reports of positive results in a high percentage of cases. On the other hand, an equally qualified group has been unable to obtain any or at most a negligible number of positive results.

It is significant that with, I believe, only one exception the microorganism obtained was Streptococcus viridans. There is considerable evidence, which will be considered later, that the disease may be due to infection with Streptococcus haemolyticus. It is somewhat significant that in the past two years there is a dearth of reports of positive results of cultures. While it cannot be decided positively at this time, there is accumulating evidence that positive results were probably due to wrong interpretations or errors in technic.

The primary source of infection in rheumatoid arthritis is still a moot question and will be discussed under treatment.

It has been suggested that the disease might be allergic. It is impossible, I believe, to explain the pathologic process on an allergic basis.

There is some evidence that a previous attack of acute rheumatic fever is a predisposing factor. There is considerable evidence that there is some relationship between the diseases. In 25 per cent of patients with rheumatoid rheumatic arthritis Dawson[16] noted subcutaneous nodules identical histologically with those observed in cases of acute rheumatic fever. This is approximately their incidence in cases of acute rheumatic fever. Glover in his report stated that 18 per cent of patients with rheumatoid arthritis give a previous history of acute rheumatic fever, but 14 per cent of patients with osteo-arthrosis also give a history of acute rheumatic fever.

It is generally reported that the disease is much more frequent in females. Anton Fischer, in his large clinic at Aachen, noted that the two sexes were equally affected.

In the Glover report it was stated that the investigators were unable to find that occupation played a rôle in the incidence of the disease. There is some difference of opinion as to whether or not heredity plays a rôle.

Climate plays an important rôle in the incidence of both acute rheumatic fever and rheumatoid arthritis. They are both diseases of north

15. Cecil, R. L.; Nichols, E. E., and Stainsby, W. J.: Am. J. M. Sc. **181**:12, 1931.

16. Dawson, M. J.: J. Exper. Med. **57**:845, 1933.

temperate zones. In the southern states both of the diseases are of infrequent occurrence. Coburn and Paul [17] reported that children in New York who were subject to annual attacks of acute rheumatic fever were free from recurrence when living in Puerto Rico. In New York, while the nasopharynx was free from hemolytic streptococci in summer, the organisms appeared in late autumn and winter. In the tropics at sea-level there is a very low incidence of scarlet fever. This is the case, for example, at Rio de Janeiro. In the same latitude at an elevation of 3,000 feet its incidence is considerably greater. Nichol [18] stated that during a period of five years only 4 cases of acute rheumatic fever were observed at the Miami General Hospital, although 31,158 patients were admitted during this period.

Clarke [19] has made a complete review of the incidence of acute rheumatic fever in the tropics. He practiced for thirty-three years in India and during this period examined 150,000 patients, but he never saw a patient with mitral stenosis, acute rheumatic fever or chorea. He also registered the births and deaths for a period of years. In 97,000 death certificates, acute rheumatic fever was never recorded. Clarke has carried on correspondence with pathologists in the tropics, one of whom had performed 600 autopsies and had never noted mitral stenosis.

Freund [20] reported that in 42 per cent of 110 cases of rheumatoid arthritis the condition directly followed acute rheumatic fever or the patient gave a history of having had that disease.

Anton Fischer observed 201 cases of secondary rheumatoid arthritis. In 65 per cent the disease was directly engrafted on acute rheumatic fever. The acute inflammation never completely cleared up, and gradually there developed the signs and symptoms of rheumatoid arthritis. In the remaining 35 per cent the acute disease subsided and was followed after a brief interval by rheumatoid arthritis. Valvular heart lesions developed in 60 per cent of this group. It is Fischer's opinion that the presence of valvular lesions in persons with rheumatoid arthritis is usually due to an antecedent attack of acute rheumatic fever.

Osteo-Arthrosis.—This is a degenerative disease due to long continued mild trauma, to acute trauma or to ligamentous traction. In the spine the acute trauma may be osteomyelitis of a vertebra. Here, gradual impairment of the disk leads to greater mobility of the vertebra, and this results in increased traction on the intervertebral ligament. Traction is the chief factor responsible for osteo-arthrosis of the spine. Acute damage to the disk or vertebra (whether this is due to external injury or to infection) is responsible for localized osteo-arthrosis of the spine.

17. Coburn, A. F., and Paul, R. H.: J. Exper. Med. **56**:609, 1932.
18. Nichol, E. S.: Am. Heart J. **9**:63, 1933.
19. Clarke, J. T.: J. Trop. Med. **33**:249, 1930.
20. Freund, Ernest: Gelenkerkrankungen, Berlin, Julius Springer, 1929, p. 75.

In the extremities all three of the factors, either singly or combined, may be responsible for the changes in the joint. Acute damage to an articulation at any age may be followed by osteo-arthrosis. I recently examined a young woman who at the age of 17 years had frozen the index and middle fingers on the right hand. They were so badly damaged that amputation was considered. However, the circulation returned, and the fingers were saved. The two fingers never grew in length, apparently owing to severe damage to the growth center in the epiphysis. Furthermore, osteo-arthrosis developed in the middle and terminal articulations of these fingers, probably owing to damage by freezing of the articular cartilage.

Overweight is the most frequent cause of osteo-arthrosis of the knee. This is met with especially in women at the menopause who have gained weight rapidly. It is frequently mentioned that this suggests an endocrine etiology of the disease. An endocrine disturbance probably accounts for the gain in weight but not directly for the osteo-arthrosis. I have examined two young, slender women with osteo-arthrosis of the knees. In both instances there had been severe injury of the knee, which was followed by synovitis. Osteo-arthrosis was caused later, I believe, by acute injury and resulting damage to the cartilage.

The so-called gonorrheal spur on the os calcis is sometimes referred to as evidence that osteophytes may be due directly to an infection. The term gonorrheal spur is a misnomer. Gonorrhea is a widespread disease. When a person who contracted gonorrhea in his youth later shows a spur on the os calcis, it would be an error to conclude that it was of gonorrheal origin. Spurs develop on the os calcis at the point of attachment of the plantar fascia. There are then two factors, pressure and traction, both recognized as etiologic factors in the formation of osteophytes. It has been demonstrated that men who stand a great deal, such as motormen, conductors, dentists and barbers, are especially prone to the development of osteophytes on the os calcis.

SIGNS AND SYMPTOMS

Rheumatoid Arthritis.—In adults the disease rarely is marked by an acute onset. In children the onset is usually acute and at times is not readily differentiated from acute rheumatic fever. In adults the onset is usually insidious, with migratory pains in the joints or slight stiffness of the fingers preceding definite inflammation in the articulation. There is a tendency to symmetrical involvement. Most frequently the fingers and wrists are first involved; next in frequency is the knee; eventually all articulations in the extremities may be affected and, in addition, the articulations of the jaw. The joints become tender, slightly swollen and painful on motion. A characteristic spindling of the midarticulation

of the fingers marks the disease. The hands become cold and clammy. The skin, because of atrophy, becomes smooth and shiny as the disease advances.

There is selective muscle atrophy, which is an important factor in the marked deformities observed in the advanced stages. The cause of this particular group of changes—coldness of the extremities, atrophy of the skin and selective muscle atrophy—is, I believe, unexplained. The coldness of the extremities and atrophy of the skin are probably due to ischemia, but no satisfactory explanation has been found for the ischemia. The selective muscle atrophy has not been satisfactorily explained. It may continue to progress after all evidence of inflammation in the articulations has subsided. Eight years ago I observed a patient with rheumatoid arthritis confined to the hands which had been present for one year. Aside from the swellings of the joints, there was no deformity. The patient was given five intravenous injections of typhoid vaccine, and the inflammatory symptoms, including pain, promptly subsided. He has not had a recurrence. He plays golf and goes duck shooting each autumn. During this period there has gradually developed marked ulnar deviation of the hand, a common type of deformity in this disease. If the disease progresses, fibrous or bony ankylosis and muscular contractions develop, which cause a marked deformity. Subcutaneous rheumatic nodules, especially in the region of the elbow, may appear. The course of the disease is extremely variable, and for this reason the results of treatment are of little value unless an untreated control series is observed. In the mild cases, even after years, the disease may not progress. Furthermore, the disease is characterized by remissions, when the improvement is marked or when the symptoms of activity may disappear entirely. Apparently the infection has been spontaneously controlled or obliterated. The question can be raised as to whether or not the recurrences might be due to activation of a chronic latent infection. In a recurrence the symptoms may develop rapidly, and within a few days the involved joints may become painful and tender. This sudden development of acute symptoms would not fit in well with the activation of a latent infection. Furthermore, such a recurrence frequently follows an acute infection of the upper respiratory tract. Later the symptoms may (and usually do) recur, because of reinfection, I believe. The infection dies out in a joint which has become ankylosed because of the complete obliteration of the synovium, the soil on which the micro-organism thrives.

Roentgenograms made during the early stages show only increased porosity of the end of the long bone adjacent to the involved joint. The cause of the early atrophy of the bone, which is akin to atrophy of the skin and muscles, has not been explained satisfactorily. Later, roentgenograms show a narrowing or obliteration of the interarticular space,

which is caused by destructive changes. Swelling of the regional lymph glands is often present. Only in the acute cases is the spleen palpably enlarged. There is usually a moderate degree of secondary anemia.

Is rheumatoid arthritis ever responsible for valvular cardiac involvement? It is reported that from 5 to 10 per cent of patients with the disease have a cardiac murmur. I cannot recall a single instance in the literature in which it was definitely determined that mitral stenosis actually appeared during the course of the disease. If a mitral regurgitant murmur develops, the question should still arise as to whether the murmur is due to involvement of the leaflets or to impairment of the heart muscle. The development of mitral stenosis during the course of the disease would be acceptable evidence that rheumatoid arthritis can be responsible for a valvular lesion. A considerable number of the patients have previously had acute rheumatic fever, chorea or scarlet fever, which might have been responsible for the stenosis.

Anton Fischer stated that in cases of secondary rheumatoid arthritis 65 per cent of the patients had valvular lesions. He had never noted a valvular lesion in a case of primary rheumatoid arthritis.

Rarely is there great difficulty in making a diagnosis except in those cases in which indefinite neuralgic pains and perhaps slight stiffness of the joints alone are present.

Rheumatoid Arthritis of the Spine.—One must bear in mind that in only a small percentage of cases is spondylitis ankylopoietica due to the infection responsible for rheumatoid arthritis. The gonococcus is responsible in a large percentage of cases. While the hip joint is rather infrequently involved in rheumatoid arthritis, it is frequently involved when the disease attacks the spine. The hip joint was involved in 19 per cent of Anton Fischer's cases. The sacro-iliac articulation is also frequently involved. In a case of rheumatoid arthritis, with its insidious progress, the patient may complain very little of his spine. His only complaint may be of slight but gradually increasing rigidity, with some pain in the nerve roots. Pressure along the spine may be painful. As the articulations of the ribs become ankylosed, the respiratory expansion of the chest is reduced. Roentgenograms of the spine may show obliteration of the interarticular spaces at the articulations of the transverse processes. When the pathologic changes progress to make a complete picture, there is characteristic "bamboo-stick" spine.

When the onset is acute, as is usually the case when the infection is due to the gonococcus, the pain along the spine and the nerve roots posteriorly may be intense. The pain in the nerves is thought to be due to direct involvement of the root as it comes into close proximity with the lateral articulations of the spine.

Osteo-Arthrosis of the Extremities.—The Heberden node is as a rule slightly tender to pressure and bending. If the node develops

rapidly, it may be quite tender. This is probably due to displacement of the soft tissues. The articulation which is most troublesome is the knee. Pathologic changes in this joint are noted most frequently in women who are overweight and especially in those in whom the obesity has developed rapidly, as, for example, after the menopause. The first symptom is usually stiffness, with perhaps slight pain on rising from a sitting posture. Later, the knees are very painful when the patient goes up or down stairs. This is due to the increased weight borne by the articulation. Standing, unless prolonged, is rarely painful. Walking on the level may not be painful.

All are so familiar with the appearance of a Heberden node that a description is unnecessary. Examination of the knee frequently shows some puffiness due to traumatic synovitis. Tenderness is not marked. By holding one hand on the knee cap and having the patient swing the leg, a crunching sensation can usually be elicited. A roentgenogram of the knee may not show a formation of spurs, as they are often very slow in forming.

In this discussion only the knee and fingers have been mentioned. In the elbow and shoulder the chief symptom is pain on making certain movements. The diagnosis of osteo-arthrosis in the shoulder can best be made by a roentgenogram, as a subacromial bursitis may cause similar symptoms. Osteo-arthrosis does not cause ankylosis, although some restriction in movement may be present.

Osteo-Arthrosis of the Spine.—Osteo-arthrosis of the sacro-iliac articulation may develop as a result chiefly of traction caused by sacro-iliac slipping. Osteo-arthrosis of the spine is more troublesome and may produce a greater degree of disability than osteo-arthrosis of the extremities. The chief symptoms are due to pains in the nerve roots—in the sacral, lumbar, dorsal, occipital and cervical portions. The etiology of these pains is not clear. Anton Fischer stated positively that the pains in the roots are not directly or indirectly due to the osteophytes. He attempted to explain the discomfort as being due to other factors, but his arguments are not very convincing.

Osteo-arthrosis of the spine is almost universal in persons past 60 years of age. Schmorl has removed 10,000 spines at autopsy and has carefully examined 4,253 spines (practically equally divided between the sexes) for osteophytes. He reported that osteo-arthrosis was not noted in the spines of subjects under 20 years of age. Between the ages of 20 and 29 it was present in 36.3 per cent; between the ages of 40 and 49, in 77.8 per cent; between the ages of 60 and 69, in 95 per cent, and between the ages of 70 and 79, in 97 per cent. There was only a slight difference at the various age periods in the two sexes.

With this high incidence, it is apparent that osteo-arthrosis of the spine only occasionally causes discomfort. Rarely does it cause a high

degree of permanent disability and then only for persons in special occupations. It is responsible, however, for many aches and pains and for considerable worry on the part of the patient, who fears that he has a disease which may cripple him.

MIXED FORMS

The presence of rheumatoid arthritis and osteo-arthrosis in the same patient has been a stumbling block in the classification of chronic rheumatism. This has even led some physicians to express the opinion that the two types of chronic rheumatism are closely related. One is able to explain most, if not all, the mixed forms if one admits that acute trauma, long continued mild trauma and ligamentous traction are etiologic factors in osteo-arthrosis. The presence of osteo-arthrosis in conjunction with rheumatoid arthritis does not mean that the osteophytes are a direct result of rheumatoid arthritis or are indirectly due to infection.

As a result of acute trauma or long continued mild trauma the patient may have had osteo-arthrosis preceding the onset of the rheumatoid arthritis. More frequently, however, the deformity produced by the rheumatoid arthritis causes unequal pressure on the articular surface and increased ligamentous tension. Ulnar deviation of the hand, a frequent deformity in rheumatoid arthritis of the wrist and hand, is frequently associated with the presence of osteophytes on the involved joints. Unequal pressure can cause osteophytes to appear on the concave side of the deformity, and ligamentous traction can explain their presence on the convex surface.

I have seen marked osteo-arthrosis of the spine of a child of 12 years who was so crippled by rheumatoid arthritis that she walked in a crouching posture. The deformity arising from rheumatoid arthritis of the ankle or foot can be responsible for osteo-arthrosis of the corresponding knee. While one may not be able in all cases to explain osteo-arthrosis associated with rheumatoid arthritis, this is not an argument that rheumatoid arthritis can be directly responsible for the formation of osteophytes. Another questionable etiologic factor in the mixed type of arthritis is the impairment of circulation, noticed especially in the skin—a possible factor in degeneration of the cartilage.

PROGNOSIS

Rheumatoid Arthritis.—Rheumatoid arthritis is inconspicuous as a cause of death, but it may be very expensive to the community when impoverished patients require hospital care. It is responsible for great physical discomfort and mental anguish. A specific form of treatment that will promptly terminate the disease in a high percentage of cases has not been developed. Even if such a type of treatment were found,

it would not prevent recurrences of the infection. This is a problem almost, if not quite, as great as that of destroying an active infection in this disease. The course of the disease is so extremely variable and a remission is so uncertain that while it may be used by the physician to encourage the patient, he is never able to predict when such a remission may occur.

Osteo-Arthrosis.—The physician can assure the patient that the probability of more than a moderate degree of disability is slight. It is true that it may disable a laborer for his particular vocation. In persons whose work requires heavy lifting, osteo-arthrosis of the lumbar portion of the spine may disqualify them for their particular jobs. With few exceptions, however, it may be considered as a painful but not a disabling disease.

TREATMENT OF RHEUMATOID ARTHRITIS

Sir William Osler said: "In treatment the placid faith of the believer, not the fighting faith of the aggressive doubter, is our besetting sin." This statement, I believe, may well be applied to the therapy of rheumatoid arthritis in the past.

It is the aggressive doubter who insists that the control method be used. Rheumatoid arthritis is a disease the onset and course of which are extremely variable. Spontaneous remissions are not uncommon, and such remissions may reach the point where all evidence of infection has subsided. In deciding whether or not improvement has followed a certain course of treatment, such improvement to be convincing should occur shortly after the treatment is instituted. Emphasis must be placed on the objective observations. A patient with an enthusiastic physician standing at his side after an operative procedure (whether it is the extraction of a tooth or the use of vaccines) is not in a state of mind to give reliable information as to the way he feels.

The first essential in successful treatment of the disease is early diagnosis, before contractures or ankylosis has developed. When these complications have appeared, while the deformity in many cases can be corrected to a certain degree, the patient rarely can expect more than a considerable degree of improvement in his condition.

The aim of treatment is: (1) to destroy the infection in the diseased joints; (2) to prevent contractures and ankylosis, and (3) to prevent reinfection.

Unless improvement is prompt after any method of treatment, the question may be raised as to whether the condition became better as a result of treatment or whether the improvement was due to a spontaneous remission. Any special treatment extending over months increases the chances of a spontaneous remission. The improvement in the patient's condition must be objective. Before the treatment is started

a careful report should be made of the joints involved and the degree and character of the pathologic changes.

The patient with a painful crippling chronic disease has faith in a magic wand that will restore his health. The patient has temporary faith in each new method of treatment and will declare he is benefited, even though examination of the joints fails to confirm the statement. An enthusiastic physician may acquire at least a temporary reputation for great skill. The psychic effect of treatment must always be borne in mind before drawing conclusions. The head of the department of medicine in a state university, wishing to make cultures from lymph glands adjacent to involved joints, sent patients to the hospital for removal of a gland. He told me that on the day following some of the patients told him how much they had been benefited by the minor surgical operation and demonstrated by movements that the treatment had been a great success. Many instances of the psychic effect of simple procedures have come to my attention. A woman with brachial neuralgia recently consulted me. One month previously she had consulted a physician, who told her the pain was due to arthritis. A roentgenogram was made, an abscessed tooth was found, and the patient was told that this was the cause of the trouble. The tooth was extracted, and by the time the patient reached home the pain had subsided. Three days previous to the time she consulted me she read of the death of a man of arthritis; her pain immediately returned.

There is, I believe, only one method of procedure which is at all dependable, namely, the use of controls. The controls must have the benefit of psychic influence, for instance, the use of measures which cannot possibly modifiy the disease but which add to the patient's hope. No doubt the thousands of persons who claim to have been benefited by Locke's manipulative treatment owe their improvement to faith.

Of the means employed to fight the infection, two will be discussed: vaccines and fever therapy.

Since the introduction of vaccine therapy, it has been used extensively in the treatment of rheumatoid arthritis. As the specific micro-organism of rheumatoid arthritis is undetermined, the vaccine used may be considered nonspecific. Most of the vaccines used have contained streptococci. Many of the reports on the use of vaccines in the treatment of this disease are of no value because no attempt has been made to separate the two types of rheumatism. Often when the physician has recognized two types of rheumatism and has treated the infective type, no attempt has been made to use controls. Dawson and Boots [12] administered treatment with various vaccines in 2,000 cases of rheumatoid arthritis. The controls were given subcutaneous injections of isotonic solution of sodium citrate, a wise procedure, as each group received subcutaneous injections. The investigators concluded that the value

of vaccine therapy in the treatment of this disease has not been proved. Remissions occurred with equal frequency in those receiving vaccines and in the controls. The workers were not able to modify the sedimentation rate with vaccine therapy.

Fever therapy, produced by the intravenous injections of the organisms of typhoid, has been in use in the treatment of this disease for more than twenty years. More recently, various other methods of raising the body temperature have been introduced. The results of this method of treatment indicate that it has some value. As the results are immediate, spontaneous remissions can be excluded. Recently, Short and Bauer [21] raised the body temperature by means of diathermy to 104 F. and maintained the temperature at this point for four hours. Eighty per cent of the patients had temporary relief, but in only 20 per cent was the relief maintained during the period of follow-up (from one month to one year). The results of these investigators parallel rather closely those of other observers who have used heat therapy: A large percentage of patients obtain temporary relief, only a small number of whom maintain this improvement for a year.

I have administered typhoid vaccine intravenously for twenty years in the treatment of this disease. About 40 per cent of the patients are entirely relieved from pain and tenderness after they have received from three to five injections, given every other day. Within a month 50 per cent have a return of the disease, because, I surmise, of incomplete destruction of the infective agent. Most of the remainder of the group have a return of the disease after several months or perhaps a year. A few of the patients have not had a recurrence during the five to ten years that have elapsed since treatment. The earlier in the disease the treatment is instituted, the better the results.

Apparently heat and foreign protein therapy are responsible for recovery from the infection in a small percentage of those treated. The later recurrence of the disease should not be used as an argument against the value of this form of therapy. A spontaneous remission is usually followed by recurrence of the disease.

Focal Infections.—Under the term focal infection is included two types: acute focal infection and symptomless chronic foci. The acute focal infections that are of special interest in rheumatoid arthritis are those of the upper respiratory tract: nasophayngitis, acute sinusitis, laryngitis and tracheitis. The chronic foci of special interest are those in the tonsils, teeth and sinuses. There is a small group of physicians who stress the intestinal tract as the source of infection. In recent years little has been written on the gallbladder and the prostate as

21. Short, C. L., and Bauer, W.: Treatment of Rheumatoid Arthritis with Fever Induced by Diathermy, J. A. M. A. **104**:2165 (June 15) 1935.

sources of chronic foci. More attention is directed toward the teeth, the tonsils and the sinuses.

Of these two types of infection, chronic foci have been considered the more important. At least these are the foci that are first attacked. Steindler [22] examined 3,000 patients with rheumatoid arthritis and 1,335 with osteo-arthrosis for evidence of chronic foci of infection in the tonsils, teeth, sinuses, intestinal tract, prostate and adnexae. Of the 522 cases of rheumatoid arthritis in which foci were found, the tonsils were infected in 55 per cent, the sinuses in 45 per cent, the teeth in 16.5 per cent, the intestinal tract in 1.5 per cent and the prostate and adnexae in 7 per cent. Of the 240 cases of osteo-arthrosis in which foci were found, the tonsils were infected in 47 per cent, the sinuses in 56 per cent, the teeth in 28 per cent, the intestinal tract in 7 per cent, and the prostate and adnexae in 5.3 per cent. Steindler reported lasting improvement after the removal of foci in 35 per cent of patients with rheumatoid arthritis and in 20 per cent with osteo-arthrosis. The value of these figures depends on how the information was obtained. Subjective information is of limited value.

It is difficult to evaluate the results of such a study. I believe that physicians will agree that from simple observation the tonsils and teeth of patients with rheumatoid arthritis are not different from those of the routine type of patient who enters a physician's office. The patients with osteo-arthrosis in this group might be considered controls, as there is no evidence that the disease is directly due to infection.

The numerous reports of favorable results after the removal of chronic foci of infection are not convincing. As a rule, this was not the only method of treatment employed but was combined with hydrotherapy, physical therapy or some other method of treatment. There is little evidence in the reports that the improvement was confirmed by objective study. A not uncommon method employed in obtaining information from the patients is by letter.

The feelings of patients with rheumatoid arthritis vary from day to day. The improvement in the patient with osteo-arthrosis can be explained on the same basis. In both groups the power of suggestion and the psychic influence of surgical intervention should be weighed.

There is considerable evidence that chronic rheumatoid arthritis is due to infection with some type of hemolytic streptococcus, as shown by the agglutination and precipitation tests. There is no evidence that Str. viridans plays a rôle.

In 1927 Rosenow reported the results of cultures of material from twenty-five granulomas from patients with various diseases. Eighty per cent showed pure growth of nonhemolytic streptococci; 12 per cent

22. Steindler, A.: Proc. Am. Soc. Control Rheumatism, 1934.

showed a mixed growth of streptococci, staphylococci and bacilli, and 8 per cent gave negative results. No mention was made of finding hemolytic streptococci. Lehman [23] made cultures from 167 granulomas. Three were sterile. The others contained various forms of streptococci (many unclassifiable), but no mention was made of the presence of hemolytic streptococci. From a single granuloma he usually noted a pure culture of a single strain of Str. viridans, but different strains were present in granulomas from different teeth of the same patient.

In experimental efforts to reproduce the pathologic process of chronic rheumatoid arthritis in rabbits, no one has produced changes even remotely resembling those of that disease. If small doses (1 cc.) of vaccine are used no changes in the joint are produced; if large doses (and these are often of ridiculous size) are used changes in the joints may be produced, but they have the character of suppurative arthritis. Even to obtain these changes young rabbits must be used. It can be said definitely that there is no experimental evidence that chronic foci of infection are responsible for rheumatoid arthritis.

There is abundant evidence that the removal of tonsils does not prevent acute recurrent rheumatic fever. Davis [24] noted that of 185 patients with a history of rheumatic fever who had their tonsils removed 77 per cent had recurrences of the disease. A statistical report by Kaiser was referred to by Davis: Of 20,000 school children who had had their tonsils removed, 8 per cent had rheumatic fever; of 28,000 children who had not had their tonsils removed, 10 per cent had rheumatic fever.

Finland, Roby and Herman [25] reported on 654 consecutive cases of acute rheumatic fever and noted that removal of the tonsils did not have any effect on recurrences. In this group 114 patients had had their tonsils removed previous to the first attack of rheumatism. Of the entire group, 43 per cent reported sore throat preceding the attack. Removal of the tonsils did not prevent sore throat.

A conservative statement can be made at the present time that there is no convincing evidence that the infective agent in rheumatoid arthritis is derived from chronic foci, and, consequently, it is probable that the foci are not responsible for recurrences. It is especially unfortunate that the removal of chronic foci is considered as the first and major treatment of the disease. This procedure is responsible for the loss of much valuable time which might be utilized more profitably in other procedures.

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23. Lehman, W.: Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1930, p. 482.
24. Davis, J. S., Jr.: Am. J. M. Sc. **186**:180, 1932.
25. Finland, M.; Roby, W. H., and Herman, H.: Am. Heart J. **8**:343, 1933.

In a disease that pursues such a variable course it is essential with any method of treatment that treated patients and a control group be observed simultaneously. Such a method is now under way at the Presbyterian Hospital in New York. Foci of infection are removed in one group, and the patients receive the same after-treatment as the controls, in whom infective foci are not treated. Dr. Dawson, who is aiding in the study, believes that in four or five years he and his associates will be able to throw some light on this perplexing question.

What evidence is there that acute infections of the upper respiratory tract are the source of infection in this disease? There is very little positive evidence. It is generally accepted that the onset of acute rheumatic fever is preceded frequently by sore throat. In the region of the nasopharynx there are no protective lymph glands to filter out the infection. The virulence of the micro-organism is probably greater in acute infections, and time is required for the development of immune bodies. In cases of chronic foci the virulence of the germ is probably lessened and the body may have acquired some immunity.

Recurrent attacks of rheumatoid arthritis are frequently preceded by colds in the head. Climate is an important factor in the incidence of rheumatoid arthritis, and there is no evidence that climate affects chronic foci.

Diet.—Many dietary fads have been recommended for the treatment of the disease. These have been adequately discussed by Bauer.[26] He concluded that the best diet is well balanced, such as that which is usually eaten by intelligent persons in good health. Patients with this disease are usually undernourished and require a full diet. There is no satisfactory evidence that vitamin deficiency plays a rôle.

Relief from Pain.—Heat applied in any manner often gives considerable relief. Acetylsalicylic acid given in moderate doses frequently repeated often will make the patient more comfortable. When the pain prevents sleep and is not relieved by the aforementioned means, ½ grain (0.03 Gm.) of codeine sulfate alone or combined with a hypnotic may permit the patient to sleep. Acetylsalicylic acid, if administered, should be given to relieve pain; it has no effect on the course of the disease.

Many patients of moderate means go to a sanatorium in order to take baths in what is reported to be water of special value in the treatment of rheumatism. The psychologic effect of such a resort may be of value, but the water has no more value than that in the home bathtubs.

The patient with rheumatoid arthritis of the weight-bearing joints should remain in bed.

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26. Bauer, W.: What Should a Patient with Arthritis Eat? J. A. M. A. **104**:1 (Jan. 5) 1935.

Sulfur Therapy.—Cawadias [27] noted that the urine of patients with rheumatoid arthritis contains excessive amounts of sulfur. It was later demonstrated that the nail clippings of patients with this disease contain less sulfur than occurs in the nails of normal persons. This gave rise to the idea that rheumatoid arthritis was due to a deficiency of sulfur, a rather speculative deduction. Cawadias stated that sulfur plays a rôle in the proper nutrition of cartilage. The recent literature contains numerous reports on the curative value of colloidal sulfur administered intramuscularly or intravenously. In none of the reports is mention made of suitable controls having been used or of careful objective study of the reputed improvement. The period of treatment is prolonged, and this gives an opportunity for spontaneous improvement.

Gold Salt Therapy.—Many papers have appeared recently on this method of treatment. Foerstier [28] reported on 500 cases of rheumatoid arthritis in which treatment consisted of the subcutaneous injection of gold salts. He reported improvement in 50 per cent of the cases in which the condition was in an early stage and in from 20 to 30 per cent of those in which it was in a late stage. The treatment extends over a long period. No controls were used, and such a report is of limited value. Treatment with gold compounds can, and often does, cause serious renal damage.

Prevention of Deformity and Ankylosis.—The prevention of deformity and ankylosis is just as important as the attempt to destroy the infection. If the infection disappears spontaneously or as a result of treatment and the patient is a permanent cripple he is still an invalid. From the onset of the disease efforts should be directed toward the prevention of deformity. If an orthopedic surgeon is available he should take charge of this phase of the treatment. If this is not possible, the general practitioner or internist in charge should direct his attention to this complication. When the synovium is destroyed and then replaced by connective tissue fixation of the joint, even for a relatively short period, ankylosis will almost certainly follow. It is important that daily gentle slight movement of the joint, adequate to prevent ankylosis, be carried out. In the acute stage of the disease complete rest, with the application of heat and moderate doses of acetylsalicylic acid, may be necessary for a few days before even slight movement can be undertaken. Deformity is due largely to muscle spasm, and experience will enable the physician to anticipate the type of deformity that usually develops. As an illustration, when the wrist is involved, ulnar deviation of the hand is a common type of deformity.

27. Cawadias, A.: Brit. M. J. **2**:602, 1926.

28. Foerstier, J.: Lancet **2**:646, 1934.

In the knee there is a tendency to marked flexion of the leg. Muscle spasm is a physiologic effort to put the joint at rest.

Heat, gentle massage and various forms of physical therapy are helpful. A baker into which the extremity can be placed is a simple and efficient way to apply heat. Light bivalved plaster of paris splints for the purpose of holding the extremity in its normal position can be applied at night or if necessary during the day. These should be removed daily or at most every second day, and the extremity should be moved gently to avoid ankylosis. The patient should be encouraged to make the movement himself. When the fingers are involved the patient should be urged to attempt to make a fist many times a day. It is much easier to prevent deformity than it is to correct it later.

This brief discussion of such an important subject is entirely inadequate. However, the treatment of this complication of rheumatoid arthritis belongs in the domain of the orthopedic surgeon.

Ganglionectomy.—Ganglionectomy, which a few years ago was advocated to relieve or prevent deformities, has been found to be of limited value. The operation is now restricted to young patients without ankylosis and is of value only when the small articulations are involved.

The Prevention of Reinfection.—Spontaneous remissions are not infrequent but may be followed later by reinfection and recurrence. There is evidence that fever therapy, in a limited number of cases, is followed immediately by the disappearance of all evidence of infection. Later, often after several months has elapsed, the disease recurs. It is probable that the recurrence is due to reinfection. If this is true, are there any preventive therapeutic measures? If such a patient during a remission would make his home in the tropics at sea-level, it is highly probable that the disease would not recur. As the disease is relatively rare in the states bordering on the Gulf of Mexico and also in the dry region of the Southwest, permanent residence in such a location would lessen the probability of recurrence. Measures to improve the patient's general health and to maintain it at a high level may be of some value.

News and Comment

AMERICAN COLLEGE OF PHYSICIANS

The Twentieth Annual Session of the American College of Physicians will be held in Detroit on March 2 to 6, 1936, at the Book-Cadillac Hotel. The president, Dr. James Alexander Miller, will deliver an address on "The Changing Order in Medicine." Dr. Walter B. Cannon, professor of physiology at Harvard University Medical School, will deliver the annual convocation oration on "The Rôle of Emotion in Disease." About fifty eminent authorities will present papers in the general scientific sessions, and clinics and demonstrations will be conducted at the Harper, Receiving, Henry Ford, Grace, Herman Kiefer and Children's Hospitals.

Book Reviews

The Carotid Sinus and the Cerebral Circulation. By Erik Ask-Upmark. Acta psychiatrica et neurologica, Supplement VI. Pp. 374, Lund, 1935.

Ask-Upmark has approached the problem of the relationship between the carotid sinus and the cerebral circulation from three angles: anatomic, experimental and clinical. Following an extensive general introduction, he describes the dissection of the carotid sinus in twenty-seven species of mammals, reptiles, amphibia and birds. The sinus is located at the origin of the internal carotid artery or its homologs. In the absence of the internal carotid artery the site is the base of the occipital artery. The sinus is innervated chiefly by the glossopharyngeal, partially by the vagus and the sympathetic, and rarely by the hypoglossal, nerves. The glossopharyngeal nerve is especially important, judging from the morphologic and physiologic evidence presented. Embryologically, this is to be expected, since the sinus is probably derived from the arterial structures of the third branchial arch, which lies in the domain of the ninth nerve. It is regrettable that microscopic studies were not made on the sinus and its innervation; the Bielschowsky technic would have been applicable to the specimens, however long they may have been fixed in solution of formaldehyde. No neurocytologic attempts were made to determine the central source of the fibers innervating the sinus.

Incorporated in the section on anatomy is an interesting, albeit lengthy and questionably relevant, discussion of the rete mirabile caroticum. Observations seem to show that this network, which is homologous to the pseudobranch of certain fishes, reaches a development in different species that varies inversely with the importance of the internal carotid artery as the chief source of cerebral blood.

The comparatively brief section on experimental work deals with direct observation of the pial vessels during stimulation of the sinus. Changes in the diameter of the vessels were variable, vasoconstriction being more common than vasodilatation. The author interprets constriction as a passive response to decrease in the systemic blood pressure. Active dilatation, when present, is dismissed as unimportant. In addition to a passive relationship between the cerebral and systemic vascular systems, he believes that there may be an active vasomotor reflex from the sinus. The path of such a reflex is obscure. On the whole, the paucity and variability of the experiments render the observations inconclusive.

Ask-Upmark attempts to correlate his observations on the sinus with various clinical conditions. In cases of syncope, which are clearly related to irritation of the carotid sinus, he believes that the cerebral changes are secondary to systemic variations. The work of Weiss and Baker, who found no similar relationship in some of their cases, is unfairly criticized on the basis that a transitory fall of blood pressure might have been overlooked. The same objection might validly be made to Ask-Upmark's experiments, since kymographic records were not made. The author considers the possibility of a relationship between the carotid sinus and epilepsy, cerebral vascular accidents and postural hypertension.

Two points of practical importance are brought out. In cases of tumor of the carotid body and in operations in the neck, sudden vascular phenomena may be related to injury to the sinus. Furthermore, Ask-Upmark has observed that during operative intervention in the cerebellopontile angle a dramatic fall in blood pressure may not infrequently occur on cutting or pulling on the ninth nerve.

In reviewing the records of four hundred and eighty-six verified tumors of the brain, operated on by Cushing, the author found that a low systolic blood pressure was a common occurrence (in 20 per cent of the cases), especially in instances of supratentorial lesion; not infrequently the reverse was found in cases of infratentorial tumor. He assumes that the presence of hypotension may be due to an involvement of the hypothalamico-hypophyseal apparatus. In attempting to link up

the hypothalamus with the carotid sinus, however, his enthusiasm has carried him beyond the known anatomic and physiologic evidence. Hypertension associated with tumors of the posterior fossa is treated conservatively, being explained by Cushing's theory of anemia of the vasomotor centra.

The work as a whole represents a great amount of personal industry during a relatively brief period and on this score is a tribute to the author's resourcefulness and ability. The investigation on the comparative gross anatomy is a distinct introductory contribution, and the compilation of an extensive bibliography will be a boon to workers in the field of cerebral circulation. The book, however, is far too lengthy for its contents and suffers greatly from poor editing, frequent repetitions and numerous contradictions. Individual publication of the separate sections would have been well advised. As it is, Ask-Upmark's attempt to mold his theories, as well as his observations, into a unified presentation against the background of the literature has resulted in a monograph which, viewed in toto, represents a superficial and rather unwieldly analysis of an intricate problem.

Child Psychiatry. By Leo Kanner, M.D., associate professor of Psychiatry, the Johns Hopkins University. With prefaces by Adolph Meyer, M.D., LLD., Henry Phipps Professor of Psychiatry, the Johns Hopkins University, and Edwards A. Park, M.D., Professor of Pediatrics, the Johns Hopkins University. Cloth. Price, $6. Pp. 527. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

In his introduction Kanner calls this "the first textbook of child psychiatry in the English language" and adds that it "is offered as an attempt to cover the entire field of children's personality disorders on a broad, objective, unbiased and practical basis." The first hundred and forty pages are devoted to basic principles, methods of examination and diagnosis and fundamental considerations regarding psychiatric treatment of the child. The remainder of the book deals with specific psychiatric disorders, many of which are, with doubtful propriety, renamed according to the peculiar nomenclature of the Meyerian school. These have been divided into personality difficulties (1) associated with physical illness, (2) expressing themselves as involuntary "part-dysfunctions" and (3) expressing themselves clearly as "whole-dysfunctions" of the individual.

Concerning the general organization of the subject matter, little criticism need be made. The separation of part-dysfunctions from whole-dysfunctions is, however, unjustifiable. For example, it is difficult to see the logic in classifying globus hystericus, aerophagia and psychogenic vomiting as part-dysfunctions merely because they are manifested in the gastro-intestinal tract, while stuttering is placed in the group of whole-dysfunctions.

Kanner is a representative of the "psychiobiologic" school of Adolph Meyer. In a short chapter on the principles of psychobiology and psychopathology he outlines the philosophic attitude of this school to the broad problem of personality disorders. The psychobiologist has a formula by which he regards the individual as a biologic unit reacting to the environment as an integrated functioning whole. Kanner is under the impression that this formula enables him to solve, or at least to ignore, the age-old enigma of mind and body, an enigma which has troubled the student of human behavior for centuries. He states: "The very moment that we recognize behavior, both overt and implicit, as a function of the total organism, the confusing contrast between body and mind, between physical and mental, no longer exists, or need disturb anyone" (p. 14). This is, of course, a complete non sequitur, and the psychobiologist who uses such an argument deceives no one but himself. That the individual functions as an integrated whole, which is more than the sum of its parts is a truism, which, however, fails to explain the respective rôles and importance of mind and body in the individual.

The psychobiologist calls himself a "pluralist," which is to say that he will accept any "explanation" of a behavior abnormality which investigation brings to

light. He sees good in all systems of psychiatric thought, but gives his allegiance to none. Thus the most diverse points of view are recognized, from those of Watson to those of Freud. Aside from philosophic objections, such a "pluralism" leads rapidly to opportunism and finally to superficiality. Unless one seeks for fundamentals one is perforce superficial, and such superficiality is sadly in evidence in this book. Many examples might be given. For example, in discussing disorders of speech, Kanner states that stuttering began in one patient "after some firecrackers exploded near her; in a boy who was threatened that his ear will be cut off; in a boy whose father also stuttered, and whose own speech disorder began when he and his parents were told that he had tuberculosis; in a boy who began to stutter when he was frightened by a dog; in a youngster whose speech trouble followed immediately a fall down stairs; in a boy whose perfectly normal speech was changed to stuttering on the morning after his first public recitation before a large audience. Interference with the use of the hand of preference was reported in a considerable number of stutterers." All these statements may be true, but they are so superficial as to deceive no one. There is no attempt by the author to understand the mechanism of stuttering, to study its psychopathology or, if one prefers, its physiopathology. There is simply a listing of insignificant antecedents, with a complete ignoring of fundamental mechanisms.

This superficiality is a fatal defect throughout the whole book. In the discussion of the "minor psychoses" (psychoneuroses) one searches in vain for any reference to psychopathology. There is likewise no attempt to deal with abnormal physiology in these states. Regarding hysteria Kanner has no theories of his own but culls from various conflicting hypotheses and adds, "There is some truth in all these theories." The discussion of the psychoses is limited to description. One is left without any psychopathologic interpretation to aid in understanding night terrors, somnambulism, pathologic lying, kleptomania and sadism and is asked to believe that these abnormalities result in a more or less haphazard fashion from such vague factors as "physical, constitutional, emotional, intellectual or environmental" difficulties. In the discussion of the behavior disturbances in chronic encephalitis there is no attempt to understand how encephalitis produces the disturbances, and the same is true regarding the mental states following trauma to the head.

The careful study of children will eventually make great contributions to the psychiatry of the future, since it is in childhood that the origins of behavior disturbances are to be found. Psychotherapy must be applied early in life to achieve its greatest results. It is unfortunate that this "first textbook of child psychiatry in the English language" should fall so far short of making fundamental contributions in this tremendously important field.

The Kidney in Health and Disease. In Contributions by Eminent Authorities. Edited by Hilding Berglund, M.D., Stockholm, Sweden, formerly chief of the department of medicine at the University of Minnesota, and Grace Medes, Ph.D., research biochemist in the Lankenau Hospital Research Institute, Philadelphia. With the collaboration of G. Carl Huber, M.D., University of Michigan; Warfield T. Longcope, M.D., Johns Hopkins University, and Alfred N. Richards, Ph.D., M.D., University of Pennsylvania. Cloth. Price, $10 net. Pp. 774, with 163 illustrations. Philadelphia: Lea & Febiger, 1935.

This volume, attractively gotten up, "is the outgrowth of a symposium on the structure and function of the kidney in health and disease which took place in Minneapolis during the summer of 1930." In putting these papers into book form an effort has evidently been made to arrange the material so as to cover the subject in a more or less systematic manner. The first section, on anatomy and physiology, including articles by Huber, Richards, Marshall, Rehberg and others, is satisfactory. In the subsequent parts of the book one has, on the contrary, a feeling of spottiness, as though one were reading a series of more or less

unrelated articles in a journal rather than a monograph. Even though many of these articles are excellent, one wonders whether the substance could not have been boiled down to a more homogeneous concentrate. First and last, the book covers rather well modern ideas about the function of the kidney and disease—probably better than any other available single volume.

Diseases of the Endocrine Glands. By Hermann Zondek. Third edition. Translated by Carl Prausnitz. Price, $11. Pp. 492, with 168 illustrations. Baltimore: William Wood & Company, 1935.

Coming from the pen of an eminent investigator in the field of endocrinology, this book could hardly fail to be of great interest. It is, in fact, a scholarly work dealing with the subject from the fundamentals up. The clinical descriptions are excellent and the illustrations well chosen. In view of all this, one is disappointed by the inadequate way in which certain phases are handled, especially therapy. The question of the use of iodine in cases of exophthalmic goiter is dealt with vaguely, and one is aghast at the directions given for the use of thyroid substance in myxedema. Even more surprising is the suggestion that parathormone be used in osteitis fibrosa cystica, and that in the discussion of the treatment of Addison's disease the use of sodium chloride is passed by with a casual sentence. The discussion of obesity is so confused as to be useless, and emphasis is placed on all sorts of drug therapy as against diet.

While the book is of interest to the advanced student of endocrine disease, one would doubt its value to the average physician seeking sound procedures in dealing with these disorders.

Kliniske studier over den digestive duodenalsaftsekretion. By Tage Christiansen. Paper. Pp. 229, with 17 figures, 46 tables and 112 protocols. Copenhagen: Levin & Munksgaard, 1933.

This doctor's dissertation contributes important data on two questions. The first is whether the individual glands (the liver, the pancreas and the duodenal glands) which pour their secretion into the duodenum are capable of adapting the nature of their secretion to the nature of the food to be digested, and the second is whether normal gastric digestion is a necessary prerequisite for normal duodenal digestion. In studying the former question Christiansen took a series of normal human subjects and by means of an Einhorn tube introduced into their duodenums chyme obtained by aspiration from the stomachs of other normal subjects. The donors had masticated and swallowed meals consisting of starch, veal or 16 per cent cream, according to whether carbohydrate, protein or fat was to be studied. This avoided many of the objections to experiments on animals and to observations on human patients with traumatic or surgical fistulas and enabled the author to control both the volume and the composition of the chyme reaching the duodenum. The resulting duodenal juice was aspirated continuously over thirty minute periods and studied for volume, color, trypsin, diastase, lipase and bilirubin. From the results of eighty succcessful experiments Christiansen concludes that two types of response can occur separately or in combination: an enzyme-rich secretion evoked by the natural secretagogs in the food and a defensive secretion evoked by the hydrochloric acid in the chyme from the stomach. He believes that the importance of hydrochloric acid in rousing the tributaries of the duodenum to the production of digestive juice has been overrated. Hence his interest in the patient with achylia gastrica. A series of thirty-two experiments on achylic patients receiving a variety of chymes, including chyme aspirated from the stomachs of other achylic patients, convinced him that the effluent from an achylic stomach contains substances which are strongly stimulating to the pancreas, that the achylic patient's pancreas responds normally to these substances and that achylia gastrica need not be accompanied by pancreatic achylia or by any other insufficiency of duodenal digestion.

Die ansteckenden Krankheiten. Edited by Dr. Max Gundel. Price, unbound, 35 marks. Pp. 641, with numerous illustrations and tables. Leipzig: Georg Thieme, 1935.

This is a German compendium on infectious diseases written by twenty-one different authors and assembled under the editorship of Gundel of the Koch Institute in Berlin. It is a most interesting compilation.

The various infectious diseases are discussed in considerable detail from the points of view of their etiology, clinical manifestations and particularly from the aspects of their epidemiology, preventability and therapy. Present conceptions regarding vaccination, the use of various antiserums and transfusions are well described. Each chapter ends with a number of references to the current literature.

The book is thoroughly German in character and gives comparatively little consideration to work on infectious diseases by other than German authors. Without doubt, however, it is an important reference book. It is well set up and clearly written. On the whole, it deserves recognition in this country and should fill competently a niche in all American medical libraries.

Therapie der Herzkrankheiten. By Prof. N. von Jagić and Dr. Ernst Flaum. Price, 10.50 marks. Pp. 331, with 13 illustrations. Berlin: Urban and Schwarzenberg, 1935.

This book emanates from the Second Medical University Clinic in Vienna. One of the authors is chief of this clinic, and the other has done much clinical and pharmacologic work in its station for diseases of the heart. The volume is designed to describe the manner in which heart disease is treated there and to contain as much practical information as possible.

The contents follow a logical arrangement. First is discussed the treatment of heart disease in general; then follow chapters dealing with the management of individual phases of heart disease, such as congestive failure, valvular disease and pericarditis. One of the engaging features of the book is that no time is spent in reviewing the literature. Von Jagić states in the preface that there are already many reliable sources for this information; he wishes to express his own views on the treatment of heart disease, founded on the experience of his own clinic. There is a certain amount of repetition, so that parts may seem unnecessarily redundant. On the other hand, there are detailed descriptions of many tricks of the trade which are worth knowing: how bowels are managed in that particular clinic, how sleep and rest are induced, how patients with cardiac disease are fed and how digitalis, strophanthin and the various diuretics are employed.

On the whole, the book is interesting. It will be well thought of in Vienna and by the practitioners there for whose benefit it was put together. Internists in America will be glad to refer to it, for it gives a clear account of how diseases of the heart are being cared for at the present in a thoroughly representative and highly respected foreign institution.